

PSYCHOSOCIAL FACTORS AND TYPE 1 DIABETES

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ABSTRACT

Introduction: Psychosocial factors have been associated with outcomes in the general population and type 2 diabetes, yet rarely in those with type 1 diabetes. We previously demonstrated that type A behavior is associated with lower mortality risk, while higher depression symptoms are associated with an increased risk. In addition, stressful life events have been previously demonstrated to lead to increased depression and poor glycemic control in those with type 1 diabetes.

Methods: We aimed to further understand the type A behavior and mortality relationship through assessment of potential mediators, moderators, and confounders, and well as by examining the different Bortner Rating Scale scoring methods using Cox proportional hazards modeling. We also investigated which psychosocial factors, including trait-anger, interacted with depressive symptoms to predict mortality, again utilizing Cox proportional hazards modeling. Lastly, we investigated whether increased life events scores were associated with high depression symptoms or a change in glycemic control using logistic and linear regression.

Results: We found that type A behavior was no longer significantly predictive of mortality after the additions of age, inflammatory markers/stress reactants, and waist-to-hip ratio, and that the item “fast eater, walker, etc.” was the best type A predictor of mortality, but also lost significance in multivariable modeling. Next, we found that increased depressive symptoms,

independent of anxiety and stress, were associated with increased mortality risk only in those with low anger scores. Lastly, we found that increased life events scores were predictive of high depressive symptomatology, but not with change in glycemic control.

Discussion: Along with the well established, physiological and diabetes care risk factors, psychosocial factors also play an important role in outcome development. These factors in type 1 diabetes were very understudied, thus this work has a large public health impact. In line with earlier theories of health locus of control, psychosocial factors may impact on mortality risk through a variety of pathways following a diabetes diagnosis. Future research should focus on further exploring these psychosocial factors as individual predictors of mortality, and examining them in a clinical trial setting to potentially improve outcomes.

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PREFACE

Dr. Trevor Orchard's Epidemiology of Diabetes Complications-Pittsburgh (EDC) Study has been vital to understanding many components of type 1 diabetes previously understudied, and thus has had substantial public health impact. We, as the longest type 1 diabetes prospective cohort study, have demonstrated the importance of considering diabetes care and biological risk factors, genetic risk factors, through Dr. Tina Costacou's work, and now psychosocial factors as well. Dr. Cathy Lloyd created a foundation for this psychosocial research by studying these factors in the first few years of the study, and I have now been able to expand her research up to 25 years later. I am extremely thankful for the EDC participants and their dedication, the invaluable education, guidance, and collaboration efforts I received from Dr. Trevor Orchard, my academic advisor and Graduate Student Researcher supervisor; the expertise and prompt assistance on many matters offered by Dr. Cathy Lloyd; the constant advice, support, and friendship offered by Dr. Tina Costacou, and the direction offered by my other dissertation committee members, Drs. Thomas Songer and Vincent Arena. I would also like to thank my family, Mark, Cindy, Matt, and Abbey Fickley, Grandma Dorothy Fickley and Grandpap Bob Baker, and Dylan Holt, my dearest companion and biggest enthusiast, for all of their love and support throughout my years in graduate school.

1.0 INTRODUCTION

Type 1 diabetes (T1D) is a significant health issue in the United States. The incidence of T1D has risen by approximately 3% per year [1], and accounts for 5% of all diagnosed cases of diabetes in the United States [2]. T1D occurs when the immune system destroys pancreatic beta cells, which are the only cells in the body producing the hormone insulin which, in turn, regulates blood glucose in the body [2]. Unfortunately, prevention of T1D is not yet feasible.

T1D is associated with short and long-term health problems. Insulin deficiency in those with T1D can lead to abnormal fuel utilization and acute complications such as ketoacidosis or weight loss [3]. Although survival in those with T1D has improved [4]–[12], the T1D population continues to be at an increased risk of several long-term complications (i.e. coronary artery disease (CAD), retinopathy, nephropathy, neuropathy, and cerebrovascular disease), and in particular, renal and cardiovascular disease [13]. Several studies have found an excess mortality in those with T1D (compared to populations without diabetes), even before the onset of complications [14]. However, a more recent study has demonstrated T1D life expectancy is now within four years of community-based life expectancy [15].

Several modifiable risk factors are now recognized for the development of T1D complications and mortality. While physiological risk factors are important, psychosocial factors may also affect T1D outcomes and care. Important psychosocial factors to consider in complication development and thus early mortality and for which we have data include

personality type, depressive symptomatology, hostility, anger, anxiety, stressful life events, and interpersonal support. The 2013 Executive Summary: Standards of Medical Care in Diabetes: 2013 stresses the importance of the psychosocial aspects of diabetes care and notes that screenings for problems such as depression, stress, and anxiety are currently poor and insufficient [16]. This further emphasizes the need for such research and screenings in the total care of T1D.

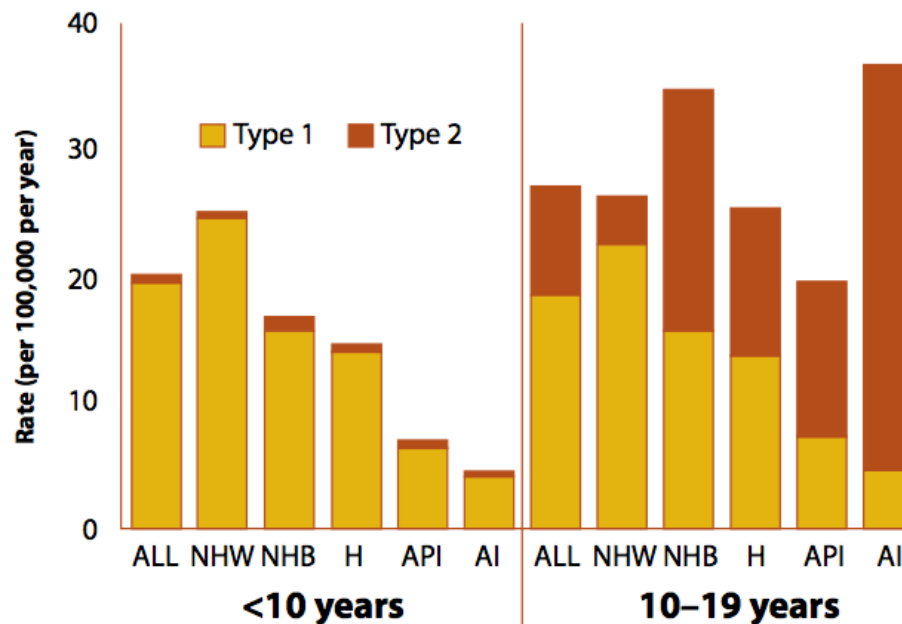
1.1 EPIDEMIOLOGY

Although T1D has been shown to be on the rise, worldwide variation exists in incidence. The best data available suggests that T1D demonstrated a stable and somewhat low incidence over the first half of the 20th century, followed by an increase that began roughly in the middle of the century [17]. This increase in incidence of T1D continues, with the majority of the rise occurring in those under 15 years of age [18].

T1D is diagnosed mostly in children and young adults, although it can occur at any age [2]. The IDF Diabetes Atlas reports that in 2010, 7.0% of people worldwide were living with diabetes, and 7.9% were living with impaired glucose tolerance (IGT) [18]. Approximately 76,000 children under the age of 15 develop T1D annually throughout the world [18]. An estimated 480,000 children globally are currently living with T1D, with 24% of these children coming from the South-East Asia region, however, European regions are at a close second, making up 23% [18].

Among those 10 years old and younger in the United States, the incidence of new T1D cases is approximately 19.7 per 100,000 per year and for those 10 years and older, there are 18.6

per 100,000 new cases per year [2]. Non-Hispanic whites have the highest rate of new cases (24.8 per 100,000 per year in those ≤ 10 years of age and 22.6 per 100,000 per year for ages 10–19) [2]. Among other racial groups (e.g. blacks, Native Americans, and Asians) T1D is less common (Figure 1) [19].



Source: SEARCH for Diabetes in Youth Study
 NHW=non-Hispanic whites; NHB=non-Hispanic blacks; H=Hispanics; API=Asians/Pacific Islanders; AI=American Indians

Figure 1: Rate of new cases of type 1 and type 2 diabetes among youth aged <20 years, by race/ethnicity, 2002-2005

Finland has the highest incidence rates of T1D in the world. In Finland, a child is almost 40 times more likely to develop T1D than in Japan and almost 100 times more likely to develop the disease than in certain regions of China [20]. The EURODIAB study, which involves a registry including 44 countries in Europe, suggests an annual rate of increase of 3-4% in incidence of T1D. A greater increase was seen in some central and eastern European countries [21]. The EURODIAB Study also noted that the largest rate of increase takes place in children 0-4 years of age. A systematic review of trends from 1960–1996 was conducted. The

investigators noted a significant rise in incidence for 24 of 37 longitudinal studies from 27 different countries (with a similar trend in another 12 studies), and only 1 study reported a small decline. The average annual increase was 3.0% [20]. A global survey suggests that no population is exempt from childhood T1D, but pointed out, importantly, a >350-fold difference in incidence rates depending on the country and region [17].

Risk factors for T1D can be autoimmune related, genetic, and/or environmental [22]. A common assumption for the development of T1D is that something novel has come in to the childhood environment to initiate T1D, such as a change in early nutrition or an infection. An alternative view is that protective factors have been lost over time [1], [23].

A nutritional aspect that has received a lot of attention is that of early introduction to cow's milk and formula based on cow's milk [24]. One study found an increased risk of T1D with early exposure to a cow's milk-based formula, as well as a short duration of breastfeeding only, and a high dietary intake of cow's milk protein [25]. Another study found similar results, demonstrating that the introduction to formula or cow's milk before five months of age resulted in an increased risk of developing T1D [26]. However, a more recent cohort study demonstrated an increased risk for T1D among those fed with cow's milk after the age of 3.8 months compared to those who were introduced to it before 3.8 months, demonstrating no increased risk of T1D by consumption of cow's milk in early infancy [27]. The Trial to Reduce Insulin-dependent diabetes mellitus in the Genetically at Risk (TRIGR), which is currently ongoing, found during their pilot study that weaning the infants from breast milk to a highly hydrolyzed formula decreased the cumulative incidence of one or more diabetes-associated autoantibodies by approximately 50% by a mean age of 4.7 years [28]. Extensively hydrolyzed formula is a formula made from casein with the proteins broken down into their basic, amino acid parts,

compared to normal formula, which contains complete proteins. The extensively hydrolyzed formula is mainly used for infants with cow's milk allergies. The possible mechanisms for this detrimental association between cow's milk and T1D are thought to involve an increase in intestinal permeability [29], inflammation in the intestines [30], and a deregulation of the immune system's response to the proteins in cow's milk [31].

In addition to the risk of T1D due to cow's milk consumption, many studies have found that breastfeeding is protective against the development of T1D, with Mayer et al. finding that children with T1D were breastfed for a shorter duration compared with healthy subjects [32]. The investigators also found that breastfeeding for 12 months or longer was protective against T1D, and another study found a marginal increased risk among children not breastfed [33]. Children, in a separate study who were younger than seven years of age, were at an increased risk of T1D when breastfed for shorter than three months as babies [34]. It is thought that the protective nature of breast milk is due to its several antimicrobial substances (e.g. lactoferrin, lysozyme, and secretory immunoglobulin A), which may offer protection against infections and viruses [35]–[37].

Viruses are another environmental exposure thought to put individuals at risk for T1D [21], [38]. A case-control study in the United Kingdom found that illness, including infections and respiratory difficulties, increased the risk for T1D in the neonatal period [39]. Several viruses, including enteroviruses [40], have been considered possible causal agents for the development of T1D [41]. New technologies have allowed for the study of enteroviruses, especially through the use of polymerase chain reaction methods to identify these viruses in the blood [41]–[45]. Studies in different countries have demonstrated that enterovirus infection accompanies or precedes the T1D onset in many children [41]. It remains unclear, however, if

this same relationship is seen in older people who develop T1D. Enterovirus infection not only in infancy, but in pregnancy, as well, has also been thought to lead to T1D [38], [41]. Prospective studies in Finland examined this relationship through studying siblings of children with T1D who were free from T1D at enrollment. Blood samples were taken every 6 months and the investigators found that enterovirus infections were found more frequently in those siblings who progressed to T1D compared to the siblings who did not. They also found that infections were clustered to the time period immediately before the detection of autoantibodies [41], [46], [47]. The mechanism behind this association is due to the initiation of islet-cell autoantibodies as well as the expression of interferon-alpha [41]. Islet-cell destruction can occur as a result of these. It seems plausible that a number of other viruses may be involved, although these associations are not yet understood.

In addition to the findings described above, the Diabetes Autoimmunity Study in the Young (DAISY), involving a genetically susceptible population versus a general population, found that the number of illnesses occurring during the first 9 months did not vary between those children with no islet autoimmunity versus those who developed islet autoimmunity for gastrointestinal illnesses, respiratory diseases, fevers, or upper respiratory symptoms [48]. They did find, however, that gastrointestinal illnesses were associated with an increased risk of islet autoimmunity among babies exposed to barley or wheat either early or late in their infancy [48]. Therefore, it appears that viruses early in life combined with the presence of inflammation caused by the diet may increase the risk of developing T1D. These findings are very interesting because they involve a combination of potential risk factors for the development of T1D, including diet, infections, and genetics.

Another important aspect of T1D development, as mentioned above, deals with genetics [21], [49]–[51]. A positive family history of T1D has been linked to a profound increased risk for the development of the disease [52], [53]. A study conducted in the United States determined that the concordance for T1D is approximately 50% for monozygotic twins, and a first degree relative has an approximate risk of 5% [54]. The occurrence of T1D among the parents of children diagnosed with T1D in the Pittsburgh study was found to be 2.6% [55]. These investigators found an increased risk to siblings of someone with T1D who experienced onset at an early age, with siblings having a cumulative risk of 0.80% by age 10, 3.3% by age 20, and 4.4% by age 30 [55]. Additional increased risk of 10.5% occurred in siblings of someone with T1D in families with at least one parent with T1D, as well [55].

The main gene associated with an increased risk for T1D is “the major histocompatibility complex (MHC) on chromosome 6, in the region associated with the genes for the highly polymorphic immune-system-recognition molecules known as HLA” [51]. HLA class I molecules present antigenic peptides to CD8 T lymphocytes, and HLA class II molecules present antigenic peptides to CD4 (helper or inducer) T lymphocytes [51]. Genetic risk further increases with the specific involvement of the DR3, DQ2, DR4, or DQ8 haplotypes, which occur in 90% of patients who develop T1D, whereas fewer than 40% of controls have these haplotypes. It was also found that DR3-DR4 heterozygosity is highest in those younger than five years of age (50%) who develop T1D and lowest in adults with T1D (20-30%). Thus, it appears that the higher the heterozygosity the earlier the onset of T1D. In addition, because those with low heterozygosity are still at risk, environmental factors must play a role in onset. The US population prevalence of this heterozygosity is only 2.4% [51]. A patient’s specific HLA

genotype can affect their ability to respond to an antigen. Therefore, the genes encoding antigen-presenting molecules are often correlated with the occurrence of autoimmune diseases [56].

There are two explanations for how the detrimental HLA genes influence the increase in risk for T1D. One theory is that these genes may affect the degree of immune responsiveness to a pancreatic beta-cell autoantigen. This would result in an overly forceful immune response which may in turn instigate damage to the pancreatic beta cells [57]. Another theory is that certain HLA genes may present the beta-cell autoantigen in a way that does not encourage normal immunologic tolerance to one's self [58]. T1D, with its complex genetic, environmental, and immunologic links, remains a challenge to explain for epidemiologists. Once the onset of T1D has occurred, individuals are at an increased risk of not only acute complications, but also major-organ complications, and ultimately mortality

1.2 RISK OF EARLY MORTALITY

People with T1D experience high mortality rates due to vascular diseases [59]–[61]. A study utilizing data from the Allegheny County childhood-onset T1D registry demonstrated that within the first 10 years following diagnosis of T1D, the leading cause of death was acute diabetes complications (73.6%) [62]. During the next 10 years, deaths were attributed to acute (15%), cardiovascular (22%), renal (20%), or infectious (18%) causes of mortality. After living with T1D for 20 years, chronic diabetes complications were responsible for >70% of all deaths. Cardiovascular disease (CVD) was found to be the leading cause of death (40%) in this population [62], as well as in others [63], and worldwide it was found that CVD causes 50% of

the deaths in T1D [64]. This is particularly seen in young adults with T1D, who may experience a 10-fold increased risk of CAD compared to the general population [65].

Glycemic control is a significant predictor of a number of acute and chronic complications, and therefore early mortality [66]. A measure of glycemic control is HbA1c which reflects average glycemia over several months [67]. The Diabetes Control and Complications Trial (DCCT) demonstrated that improved glycemic control was associated with lower rates of microvascular and neuropathic complications [68]. The Epidemiology of Diabetes Interventions and Complications (EDIC) study, a follow-up study of the DCCT cohort, demonstrated a continuation of this effect in the previously intensively treated group, even though their glycemic control became the same as that of the standard care group during follow-up [68]. This demonstrated that the effects of tight control earlier on might offer protection in the long term. In addition, cardiovascular outcomes were also reduced in the intensively treated arm [69]. The physiological risk factors for early mortality in people with T1D have been well established; however, how psychosocial factors contribute to this increased early mortality risk is understudied.

1.3 TYPE A BEHAVIOR

Type A behavior has been described as an action-emotion complex, such that the behavior is a response to the outside environment [70]. People characterized as having type A behavior tend to focus toward achieving and accomplishing more in less time than others. Because of these tendencies, these people are inclined to be competitive, aggressive, time urgent, work-oriented, and can become annoyed if things are not achieved in a time frame they find

sufficient [70]. Therefore, it seems that type A behavior is a result of predispositions within a person that are exhibited due to specific environmental cues [70].

In an earlier review regarding type A behavior and coronary heart disease (CHD), Matthews et al. noted that although type A behavior was directly associated with CHD in the general population, the findings were consistently inverse in chronic disease populations, suggesting a protective effect [70]. A review of the literature examining psychosocial variables and CHD suggested that type A behavior and hostility were only associated with CHD in less than half of the studies using healthy populations at baseline, and were associated with CHD in 13% of prognostic studies leading them to conclude that there was no consistent evidence linking type A behavior and CHD [71]. In terms of the literature specific to non-diabetes populations, it appears that type A behavior may have different effects on health depending on underlying chronic disease status and the definition of type A behavior.

Type A behavior has been demonstrated to be protective against a number of complications present in those with T1D [72]. In addition, type A behavior has been linked both positively and negatively to glycemic control, and this is most likely due to differences in study design and measurements of type A behavior and glycemic control [73]. Furthermore, these early studies lack the covariates necessary to identify the population differences. Whether T1D is an additional high risk group in which the inverse association between type A behavior and health outcomes, i.e. complications and mortality, remains conflicting in the literature [73]–[79]. Furthermore, one of the main objectives in the management of T1D is the achievement of adequate glycemic control [80], and whether type A behavior plays a role in this relationship is inconclusive. One explanation of the inverse relationship may be that higher type A behavior is

related to better glycemic control and lower complication rates due to the high-achieving, more meticulous nature of those with type A behavior.

A study performed by Lloyd et al. in the EDC study investigated whether psychosocial factors were cross-sectionally associated with diabetes related complications [81]. Investigators found that the number of complications was significantly related to participants' type A behavior score, with lower type A behavior being related to more complications. Additionally, those with the lowest type A behavior scores had higher rates of retinopathy and macrovascular disease. The study authors concluded that type A behavior demonstrated a protective effect against the number of prevalent complications and note that this association needs to be re-examined in a prospective study. A limitation of this study was the cross-sectional design, and therefore temporality could not be established.

A more recent study prospectively examined the relationship between psychosocial variables and diabetes related outcomes in those with T1D [82]. This was the first study to utilize a prospective design in investigating personality type in T1D. Among the questionnaires distributed to study participants was the Eysenck Personality Questionnaire (EPQ-R). The EPQ-R consists of 48 items and measures three dimensions of personality, including extraversion (such as sociability and optimism), neuroticism (such as negative emotions, anxiety, and moodiness), and psychoticism (such as acting hostile and lacking empathy).

The study investigators found a marginal inverse correlation between neuroticism at diagnosis of T1D and glycemic control 12 months later. The authors suggested that higher neuroticism is related to better glycemic control. The study authors hypothesize that this effect may be due to neuroticism being associated with participants having a “greater tendency to worry about the future effects and consequences of diabetes” [82]. Utilizing correlations for this

portion of the analysis is a limitation, as this method does not take into account possible confounders; however, the directionality of the relationship between neuroticism and glycemic control proves to be the same as in the study by Lloyd et al discussed above.

The most recent work regarding type A behavior in a T1D population, also performed in the EDC Study, was able to investigate type A behavior prospectively [83]. The objective of the study was to determine whether type A behavior predicted all cause mortality and incident CAD, as well as CAD-related mortality among those with prevalent CAD. Twenty-two year follow-up data from the EDC study were analyzed for the participants who completed the Bortner Rating Scale (measuring type A behavior) and Beck's Depression Inventory (BDI) at baseline (1986-1988). We demonstrated an inverse univariate relationship between Bortner scores and all cause mortality, however, the addition of BDI scores attenuated the relationship and a significant interaction was observed, such, that any protective effect against mortality was limited among individuals with lower BDI scores (bottom 3 quintiles), while no effect was seen in those with higher BDI. Strengths of this study were that it was the first to investigate the relationship between type A behavior and all-cause mortality in a T1D population, as well as the long length of follow-up time, large sample size, and complete data obtained for the population. One limitation was the minimal covariate list. Future research should focus on understanding this relationship through an evaluation of potential mediators, covering a wide range of diabetes-related risk factors for early mortality. In addition, because there is some evidence that resulting health outcomes varied according to which measurement of type A behavior was utilized, the different scoring methods of type A behavior should be examined, as well.

In conclusion of the overall T1D literature regarding type A behavior and health outcomes, only the last three papers published were completed with adequate sample sizes, and

therefore hold more weight in terms of their validity compared to the previous literature. However, the older papers found either null or detrimental affects of type A behavior and glycemic control, which differs from the conclusions drawn from the more recent studies. Based on this information, increased type A behavior may be protective against poor glycemic control and complications in people with T1D, and perhaps it has no association with health outcomes in the general population, but further research is needed to confirm or deny these inferences. Whether or not type A behavior predicts mortality in people with T1D requires further, more in-depth investigation. In particular, studies with large sample sizes investigated prospectively with a complete list of potential mediators and multivariable analyses will be important in deciding whether an effect of type A behavior on health outcomes truly exists. In addition, investigating how the different type A behavior scoring methods relate to mortality would make an important contribution to the literature.

1.4 DEPRESSIVE SYMPTOMATOLOGY

Depression affects a large portion of the population, with a lifetime risk of major depressive disorder of approximately 16.2% [84]. Discouragingly, in a survey of the 48 continental U.S. states, only 51.6% of 12-month depression cases (that is, long lasting depression for at least 12 months) were found to be receiving health care treatment, and out of these people, treatment was adequate in just 41.9%. This results in only 21.7% of 12-month depression cases having adequate treatment [84]. Being female, a homemaker, classified as "other" for employment status (most were unemployed or disabled), never married, previously married,

having less than 12 years of education, and living in or around poverty were all associated with an increased risk of either 12-month depression or lifetime depression [84].

Prevalent depression puts individuals at a higher risk of comorbid physical conditions, as well. A recent meta-analysis found that depression was significantly associated with increased stroke morbidity and mortality [85]. A separate study prospectively studied whether depression was associated with the risk of developing type 2 diabetes (T2D), and vice versa, and investigators found that during 10 years of follow-up, both depressed mood and use of antidepressants increased the risk of developing T2D [86]. In addition, those with T2D were at a significantly increased risk of developing clinical depression, regardless of treatment via oral hypoglycemic agents or insulin.[86] Major depression has also been shown to cause a 60% increased risk of hypertension [87], and a review of the literature demonstrated an increased risk of CVD morbidity and mortality in those with depressive symptomatology or major depression, as well [88].

High prevalence of depression and the comorbidities that occur along with it result in detrimental economic effects not only due to the health care necessary for treatment, but due to the loss of work performance, as well [89]. A nationally representative U.S. sample of workers found that major depressive disorder resulted in 27.2 lost workdays per year for each worker with depression [90]. This study also found that there were approximately 225.0 million workdays and \$36.6 billion in productivity lost per year due to major depressive disorder [90].

The importance of depressive symptomatology in T1D has been demonstrated: those with high depressive symptomatology are at an increased mortality [91] and morbidity risk (including diabetes complications) [92]. Co-morbid depression and T1D is also associated with poorer diabetes self-management and metabolic control, decreased quality of life, and higher

healthcare usage [91]. In addition, one study found that those with T1D were over three and a half times more likely to have depression, were over two and a half times more likely to have a history of depression, and were two times more likely to be on an antidepressant than their controls free from T1D [93]. A U.K. study found that the prevalence of depression was three-times higher in those with T1D compared to those free of diabetes [94].

It has been demonstrated that depressive symptomatology plays an important role in the incidence and progression of diabetes associated acute and chronic complications. In addition, diabetes itself appears to play an important role in the development and progression of depression. The EDC study's previous research has demonstrated that duration, hypertension, waist-to-hip ratio (WHR), physical activity, and depressive symptomatology were all significant independent predictors of CAD in women [95]. Depressive symptomatology was not a risk factor for CAD in men initially [95], but this relationship was demonstrated in both sexes in a more recent EDC study [96]. This more recent EDC study showed that increased BDI significantly predicted CHD even after controlling for hypertension, WHR, white blood cell count, fibrinogen, smoking status, distal symmetric polyneuropathy, and overt nephropathy. However, this relationship became attenuated after the addition of all possible variables in the mediation analysis [96]. Depressive symptomatology has also been found to be associated with increased WHR in both genders [97] as well as with macrovascular disease and a higher number of complications [98]. Based on these study results, depressive symptomatology is a demonstrated risk factor for poor outcomes in those with T1D. It seems that elevated depressive symptomatology can be an immediate risk factor for markers of illness, such as WHR, and in addition, affect long-term health as well. Perhaps in some instances, elevated depressive symptomatology does not demonstrate detrimental effects until a longer period of time has

passed, like with CAD in men. It may be important to identify increased depressive symptomatology early, especially when in combination with other risk factors, such as an increased WHR, to intervene before the onset of serious complications.

Regarding the existing research on depressive symptomatology and subsequent risk of mortality in T1D, only two studies have been performed thus far. The FinnDiane Study Group concluded that in women, prior antidepressant agent purchase (their surrogate marker for depression) was associated with an increased mortality risk [99]. In the EDC study, we were recently able to replicate these results; however we found the association between self-reported depressive symptomatology and mortality in both men and women, with an almost three-fold increased risk of mortality with clinically important depressive symptomatology ($BDI \geq 16$) [100]. Whether other relevant psychosocial variables interact with depressive symptomatology to predict mortality, however, is unexplored.

Depression and diabetes have an interwoven relationship. Perhaps the mechanisms underlying depression and T2D have reciprocal effects, through which each can affect the other [101]. In addition, there may be other risk factors that put an individual at risk for both diabetes and depression [86].

It has been difficult to disentangle the role depression plays in T2D due to the bi-directionality, but this has been thoroughly demonstrated to cause an increased risk of morbidity and less so, mortality, in T1D. Because T2D can be managed with lifestyle changes or oral agents, and most often the body continues to produce some insulin, the demands of care may not be equal to those of T1D, especially at diagnosis. Those with T1D have the difficult task of caring for a chronic disease, which requires maintenance multiple times a day, as well as living with the stress and fear of T1D complications due to the disease often being diagnosed in

childhood or adolescence. Unfortunately, these fears regarding future complications can lead to depression, with depression itself increasing the risk of complication development and progression. As discussed below, in combination with depression and type A behavior, hostility, anger, anxiety, life events stress, and interpersonal support may play important psychosocial roles in predicting health outcomes, as well.

1.5 ADDITIONAL PSYCHOSOCIAL MEASURES

While type A behavior and depression are the most commonly studied psychosocial factors in T1D, there are other potentially important psychosocial factors to consider, as well, which have shown health effects in other populations. Hostility is usually explained as “a negative attitude or cognitive trait directed toward others” [102]. Hostility does, however, differ from anger, which is described as “an emotional state that consists of feelings that vary in intensity from mild irritation or annoyance to intense fury or rage, and aggressiveness as a verbal or physical behavioral pattern manifest in yelling, intimidation, or physical assaults” [102]. Hostility has also been defined as “a multidimensional personality trait, the most common components of which are (1) cynicism, or the belief that others are motivated primarily by selfish concerns, and (2) mistrust, or the expectation that people are likely to be hurtful and sources of mistreatment” [103]. Hostility and anger are oftentimes combined or used interchangeably when in fact they are separate constructs and should be examined as such. It has been explained that “hostility is distinct in that it refers to a cognitive trait, in contrast to anger, which is an emotion” [103].

Since the 1980s, hostility has been linked to an increased risk of CHD [104]; however, only recently was a systematic review/meta-analysis conducted examining this relationship in prospective cohort studies. The investigators found, via their subgroup analyses, that the Minnesota Multiphasic Personality Inventory (MMPI) and its derivative, the Cook-Medley hostility scale (CMHS) were significantly associated with CHD in healthy and existing CHD studies, with increased hostility resulting in an approximate 20% increase in CHD risk in both populations [102]. Investigators also found that this relationship was more prominent in men.

Possible mechanisms that may explain this relationship are 1) behavioral pathways, such that hostility causes individuals to partake in detrimental health behaviors such as poor diet, less physical activity, smoking, inadequate sleep, or poorer self care 2) direct physiological pathways, via autonomic nervous dysregulation, increases in inflammatory and coagulation factors, and higher cortisol circulation [102].

Because hostility is such an important predictor of health outcomes, specifically cardiovascular disease (CVD), it may play a role in complication development in people with T1D. The existing literature investigating the effects of hostility within T1D is extremely limited. One study conducted in a population of African-Americans with T1D found that the development of hypertension over a 6-year follow-up period was independently predicted by hostility and overt proteinuria [105]. These findings highlight the importance of combining physical and psychosocial factors in the prediction of disease development. An additional study done in this same African-American population found that female gender, childhood trauma, and hostility were significantly associated with having attempted suicide (as was depression in a separate model) [106]. Additionally, those with T1D were more likely to attempt suicide than

the controls. Whether depression and hostility interacted to predict suicide attempts was not studied.

Investigators in the Netherlands demonstrated that those T1D participants with a high hostility score exhibited an increase in anger during hypoglycemic episodes compared to those with low hostility scores [107]. However, this study was performed with a very small sample size of 10 and therefore it is difficult to draw conclusive results. This very limited literature suggests a trend similar to that seen in the general population; that is, hostility is detrimental regarding health outcomes in T1D. Thus, studying our main predictors (those we have previous evidence in our population are associated with mortality), type A behavior and depressive symptomatology, in combination with hostility in those with T1D would fill a significant gap in the literature.

Anger, which is often examined with hostility but exists, as explained above, as its own construct, is an additional psychosocial area of focus in the literature. Most commonly, anger is broken down into two constructs: trait-anger and state-anger using Spielberger's validated and popular questionnaire [108]. Trait-anger refers to anger that comprises part of one's personality [108], whereas state-anger is anger experienced as a reaction to the surrounding environment. Other common characteristics involve keeping anger to oneself ("anger-in"), taking anger out on others ("anger-out"), or discussing anger with a friend or family member ("anger-discuss"). The physical manifestations of anger can involve, for example, developing a headache or feeling weak, and these are known as "anger-symptoms" [109].

Similar to hostility, anger has been linked to CVD events, as well. The Framingham Study used the anger-in, anger-out, anger-discuss, anger-symptoms, and state-anger constructs to investigate the association with CHD, atrial fibrillation (AF), and total mortality. In age-adjusted

analyses, they found no association of anger with the development of CHD; however, increased trait-anger and anger-symptoms in men predicted AF at the 10-year follow-up [110]. Anger was measured using both the original Framingham scale [109] and with the Spielberger scale. Increased trait-anger was also associated with AF and total mortality in men in multivariable analyses [110]. No associations between any of the anger variables with CHD, atrial fibrillation (AF), or total mortality were seen in women. Whether anger is associated with mortality in people with T1D has not been studied. In addition, whether anger interacts with type A behavior and depressive symptomatology in predicting mortality has not been studied, either. A meta-analysis investigating psychosocial variables and their association with CHD found that anger was associated with increased CHD events in healthy population studies as well as in those with existing CHD [102]. This association was more common in men compared to women, which has also been demonstrated previously with hostility. Furthermore regarding this sex difference, a recent meta-analysis demonstrated that anger and hostility were associated with cardiovascular responses to psychological stressors more strongly in men compared to women [111]. This suggests that the additive effect of daily, increased stress responses might have pathophysiological significance for CHD in men only.

As discussed previously, it is essential to investigate psychosocial factors in combination with one another, and importantly a Canadian study examined the role anger played in generalized anxiety disorder. Anxiety is another important aspect of psychosocial factors and their involvement with disease progression and development [112]. Investigators used the Generalized Anxiety Disorder Questionnaire, the State-Trait Anger Expression Inventory, and the Aggression Questionnaire, and found that generalized anxiety disorder significantly differed from participants free of anxiety regarding higher levels of trait-anger and internalized anger

expression. Participants with generalized anxiety disorder also significantly differed from those free from anxiety on the combined aggression subscales [112]. These results further emphasize the importance of examining psychosocial factors together. Furthermore, this work was performed in non-T1D populations, additionally emphasizing the need for psychosocial factors to be examined together in a T1D population, where such literature is severely lacking. The psychosocial risk factors may predict outcomes differently in a T1D population, thus it is difficult to determine that the same effects demonstrated in the general population would be demonstrated in T1D. For example, people with T1D may not be anxious by nature, but are anxious due to a fear of complications, thus perhaps their anxiety would interact with anger differently than in the general population.

Generalized anxiety disorder is defined as the presence of continuous and excessive worry, differing from the diagnosis of major depressive disorder which results in depressed mood or loss of interest [113]. The DSM-IV criteria for generalized anxiety disorder involves restlessness/agitation, fatigue, concentration difficulties, sleep problems, and irritability [113]. One study found that generalized anxiety disorder was prevalent in 5.3% of their stable CAD population [113]; investigators also found that within their participants with stable CAD, anxiety and depression resulted in increased odds of having a cardiac event over two years of follow-up, even after multivariable adjustments [113].

As expected, anxiety is more prevalent in the diabetes population than in the general population [114]. A study in the U.K. examined the relationship between generic and diabetes specific psychological factors and their impact on glycemic control in participants with T1D. Investigators found that anxiety was predictive of HbA1c, even after controlling for relevant demographic and medical covariates [115]. They also found that diabetes related distress was a

significant predictor of HbA1c. Because they initially found that anxiety was correlated with diabetes specific distress, mediation analysis was performed [115]. Diabetes related distress attenuated the relationship between anxiety and HbA1c. Authors stress that “[t]he experience of anxiety is likely to be linked both to the cognitions initiated by the awareness of the adverse long-term health consequences of sub optimal metabolic control and the experience of hypoglycemic episodes” [115]. Whether anxiety interacts with type A behavior and depressive symptomatology to predict health consequences, specifically mortality, in T1D has yet to be determined.

An additional psychosocial factor that has been demonstrated to impact health in the general population as well as in people with T1D is life events stress. Previous literature has established a strong association between stressful life events and major depressive episodes in short term [116] as well as long term follow-up [117]. In addition, stressful life events have been associated with poor health outcomes, including cancer [118] and mortality [119].

Because we have previously demonstrated a relationship between depressive symptomatology and mortality, we were interested in whether stressful life events increased depressive symptomatology in T1D populations, however this literature is extremely limited. Specific to T1D, a cohort of African American participants found that those reporting greater incidences of childhood trauma were more likely to experience depressive symptomatology [120]. In addition to the potential impact of stressful live events on depressive symptomatology in diabetes, there is concern for whether stressful life events impact change in glycemic control, as well. HbA1c is an important risk factor for complications and early mortality in those with T1D, as discussed above. Elevated HbA1c levels predict an increase, sometimes drastically, of chronic T1D complications [121]. Previous research has also shown that stressful life

experiences were associated with maintained poor control or deterioration of control in those with T1D [122]. The authors note, however, that these results require replication in a larger study population and in those with diabetes-related complications, as well.

Stressful life events involve stressors in the environment, and in addition, social support is another psychosocial construct in the external environment. Social support refers to the network of family and friends surrounding a person. Not unlike the other psychosocial variables discussed previously, social support has been shown to be associated with health outcomes, as well. A review and meta-analysis investigating social support and the prognosis of CHD found that after controlling for relevant covariates, increased social support remained significantly predictive of lower all-cause mortality in those with prevalent CHD [123].

A separate study (WISE) which combined several psychosocial variables in order to assess whether they were associated with CVD risk factors, found that depression, social network index, and the hostility component were significant independent variables [124]. Another trial studied the effects of treating depression and low perceived social support on the clinical outcomes after participants suffered an MI (Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) Randomized Trial) [125]. Investigators found that those who received the cognitive behavioral therapy, and SSRIs when needed, had improvements in depression and perceived social support compared to those in the usual care group change. However, they did not find a significant difference in those surviving event free between the two groups. The literature regarding social support in those with T1D is currently limited. Social support may prove to be important in those with T1D, as it has shown to be beneficial in chronic disease populations [123]. Because of the daily maintenance required to care for T1D, perhaps

increased social support, whether from peers with T1D or from family members, assists those with T1D in coping with their disease.

A review study on social support and its effects on different health risks in those with diabetes was performed; however, a limitation of the study is that it does not distinguish between T1D and T2D [126]. The investigators concluded that peer support demonstrated some potential to improve diabetes related outcomes; however, the existing evidence is too inconsistent and sparse to maintain an overall consensus [126].

A pilot study investigated social support in those with T1D, implemented in a professionally-run (via a clinical psychologist) support group for youth with T1D making the transition to care [127]. Investigators found that participants mainly wanted to converse about how others manage their T1D in day-to-day life, the interactions experienced with those who do not have T1D, and the emotions one experiences related to their T1D [127]. This pilot study offered important feedback about the importance of social support for people with T1D and future psychosocial research should focus on including social support as a predictor in this population. Because social support has been demonstrated to have potential importance for people with T1D, support should be taken into account when behavior type and depressive symptomatology are investigated as perhaps depressive symptomatology operates differently in the presence of high social support compared to low support. Furthermore, high type A behavior combined with high social support may potentially be more protective than type A behavior alone.

In conclusion, hostility, anger, anxiety, life events stress, and social support all have been associated with health outcomes in the general population and within those with T1D; however this literature investigating psychosocial factors in T1D is very limited. CVD outcomes appear

to be the most prevalently studied, while mortality is rarely studied. A reoccurring theme within the literature is the web these factors form with one another and how different combinations can affect health outcomes uniquely. Thus, our research focused on studying type A behavior and depressive symptomatology in depth, and in the context of other psychosocial factors in terms of mortality prediction in those with T1D (Table 17).

2.0 TYPE A BEHAVIOR AND MORTALITY IN T1D: MEDIATORS, MODERATORS, AND CONFOUNDERS

As discussed above, we have previously demonstrated that those with T1D and a higher type A behavior score had a lower all-cause mortality rate compared to those with a lower type A score. Thus, our first aim is to further understand this relationship by examining the extent to which the type A behavior and mortality relationship is mediated, moderated, or confounded by diabetes related and general health risk factors.

2.1 INTRODUCTION

T1D continues to be a significant public health and clinical issue, with the incidence of T1D rising by approximately 3% per year [1]. Excess mortality has been documented in children with T1D, even before the onset of late, chronic complications [14], although more recent research has demonstrated that T1D life expectancy is now within four years of community-based life expectancy [15]. Despite the improved survival [4]–[12], those with T1D continue to be at an increased risk of developing several long-term complications (i.e. CAD, retinopathy, nephropathy, neuropathy, and cerebrovascular disease (CBVD)), as well, as renal and CVD) [128], [129]. Thus, the search for modifiable risk factors for T1D mortality and complications remains important.

Type A behavior is a trait that has not been extensively examined as a risk factor in T1D mortality and complications. People characterized as having type A behavior tend to exhibit behaviors such as focusing on achieving and accomplishing more in less time than others. Because of these tendencies, these individuals are often competitive, aggressive, time urgent, and work-oriented [70]. These type A behaviors are thought to be inherent within a person and not solely due to environmental triggers [70]. It has been previously demonstrated that in those with T1D, glycemic control differs by behavior type (A/B), and this has been reported in both directions, with type A behavior predicting both poor control and good control [75], [130], [131]. In contrast to type A behavior discussed above, those with type B behavior are thought to generally live with lower stress and tend to work more steadily, enjoying achievement but not becoming stressed over it.

We have previously reported a relationship between type A behavior and mortality in a T1D population. Participants in a study population of individuals with T1D with higher type A behavior had a lower all-cause mortality rate compared to those with a lower type A score, an effect that interacted with depressive symptomatology such that type A behavior was only protective in those with low depressive symptomatology [83]. We proposed that this may be due to individuals with type A behavior being better able to cope with the intense regimented control needed in T1D (perhaps due to being able to do many things at once, such as thinking ahead regarding doctor visits, and feeling ambitious or motivated regarding the care and treatment of their T1D (e.g. testing blood sugar, adjusting diet and insulin dose)) [132]. This conclusion, that type A behaviors may increase the efficiency with which an individual cares for their T1D, therefore reducing the risk of early mortality, however, has not yet been confirmed from research evidence.

The goal of this paper is to further our understanding of how type A behavior protects against mortality with the following objective: to examine the extent to which the type A-mortality relationship is mediated, moderated, or confounded by other factors both diabetes and non-diabetes related (i.e.: demographic, behavioral, diabetes care, physiological measures, and depressive symptomatology).

2.2 METHODS

This evaluation is focused on participants in the EDC study, comprising individuals diagnosed with T1D between 1950 and 1980 at age <17 years, and seen within one year of diagnosis at Children's Hospital of Pittsburgh. Biennial follow-up of the EDC study cohort has occurred since baseline in 1986-1988, and included questionnaires with physician examinations and laboratory analyses of urine and blood for the first 10 years and again at 18 years and 25 years. Data up to 22-years of follow-up are now available. Participants ≥ 18 years of age at study baseline who completed the Bortner Type A Rating Scale (1986-1988) [132] were eligible for the study.

Overall total mortality, including complication status, was determined as of February 25, 2011 through contact of next of kin and searches in both the Social Security Death Index and the National Death Index. Death certificates were obtained to confirm each death, as well as: 1) hospital records; 2) autopsy/coroner's reports; and 3) interview with next of kin regarding the death.

The following baseline covariates were examined in detail based on prior evidence from the EDC study of their relationship with diabetes complications and mortality [83], [133]: age,

sex, duration, education, calories consumed, physical activity, smoking status, insulin dose, frequency of blood glucose testing per week, hypertension, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol, lipid medication use, white blood cell count (WBC), fibrinogen, WHR, HbA1c, and depressive symptomatology. Education was assessed using a 5-point scale, i.e.: some high school, high school graduate, some college, bachelor's degree, graduate education beyond bachelor's. Daily calories consumed were obtained through use of the Willett Food Frequency Questionnaire averaged over a week [134]. Physical activity was assessed using questions about current levels of leisure activities and was expressed as total kilocalories expended [135]. Smoking status was defined as having smoked more than 100 cigarettes over their lifetime. Insulin dosage was expressed as the number of units of insulin used per day divided by the participants' weight in kilograms.

Testing per week was reported as the number of times blood glucose levels were tested each week. Hypertension was defined as systolic blood pressure (SBP) greater than or equal to 130 or diastolic blood pressure (DBP) greater than or equal to 80 or on blood pressure medication. Fasting blood samples were assayed for lipids, WBC count, and fibrinogen as previously described [136]. Fasting blood samples were also analyzed for HbA1 (microcolumn cation exchange; Isolab, Akron, OH, USA), and these original HbA1 values were converted to Diabetes Complications and Control Trial (DCCT)-aligned HbA1c for all analyses using a regression equation derived from duplicate assays ($\text{DCCT HbA1c} = 0.14 + 0.83[\text{EDC HbA1}]$). WHR was calculated by measuring at the smallest circumference of the natural waist and by measuring the hip circumference at the widest part of the buttocks or hip. Finally, depressive symptomatology was measured using the Beck Depression Inventory (BDI), also collected at

baseline [137]. BDI scores have been shown to approximate clinically significant symptoms of depression [137].

The Bortner Type A Rating Scale (1986-1988) [132] is comprised of 14 items that are each composed of two phrases between 1 and 24 equally set apart scale points on a horizontal line, ranging from less type A to more type A, and respondents were asked to mark on the line where they believed they fell in terms of their own behavior (ex: always rushed vs. never rushed, even under pressure). The score obtained from each of the 14 items was added up and type A behavior was assessed as a continuous variable with the higher the score representing higher type A behavior.

Cox proportional hazards models were utilized to examine the univariate relationship between baseline Bortner Score and overall mortality and to examine the prospective associations between the baseline covariates (potential mediators, moderators, or confounders) and mortality. Next, Student's t-tests or Wilcoxon rank-sign tests were used as appropriate to assess the univariate associations between Bortner score and these potential covariates. Significant covariates were then grouped into five main risk factor categories to investigate which pathways may explain the relationship between Bortner Score and mortality: demographic, behavioral, diabetes care, physiological measures, and depressive symptomatology. Those covariates that maintained significance in the five separate multivariable models were then entered into a final, composite model of Bortner score and covariates predicting mortality, and this model is the one reported. Influential covariates were also examined to assess if they were mediating, moderating, or confounding the previously reported Bortner score relationship based on the following approach.

We determined confounding to be present if the covariate was a known risk factor for mortality and was associated with Bortner score, but was not thought to result from Bortner score [138]. If the covariate was intermediate in a causal sequence such that Bortner score influenced the covariate and the covariate affected mortality risk, then we concluded that the covariate was a mediating variable [139]. If the relationship between Bortner score and mortality differed at different values of the covariate, then we determined that the covariate was a moderating variable. Furthermore, we assessed whether the moderator was directly affecting the pathway between Bortner score and mortality, or if it was an antecedent moderator, meaning that it contributed to both Bortner score and mortality. The main difference between mediating and moderating variables is that the mediating variable specifies a causal relationship between Bortner score and mortality while the moderating variable affects the relationship between Bortner score and mortality across different levels of the covariate [139]. To determine if formal modifying was present we tested for a significant interaction between Bortner score and a covariate in predicting mortality. If a covariate significantly predicted mortality and was significantly associated with Bortner score, but was not thought to be biologically plausible as a mediator, we designated it as a confounder. The same approach was used to assess type A behavior and mortality by sex.

2.3 RESULTS

At the EDC baseline exam, of the 595 participants aged 18 years or older, and thus eligible for the BDI and Bortner questionnaires, 100 were excluded due to missing covariate measures: predominantly the Bortner and BDI questionnaires and physical activity measures.

Those excluded from analyses had a higher WBC count ($p<0.01$); were younger ($p=0.03$); had a larger WHR ($p=0.03$); were less likely to have an education greater than high school ($p<0.01$); were more likely to have ever smoked ($p=0.01$) and were more likely to be male ($p=0.04$), but did not differ for age, duration, insulin dose, testing per week, physical activity, hypertension, fibrinogen, HbA1c, non-HDL, HDL, calorie intake, Bortner score, or BDI score.

Out of these 495 remaining participants, there were 125 deaths (25.2%). These 125 participants differed from the survivors for most covariates (Table 1). Those who died were older, had a longer duration, higher HbA1c, higher WBC count, were less physically active, had a greater WHR, higher fibrinogen level, lower HDL, higher non-HDL, were more often smokers, had higher depressive symptomatology, were more likely to be hypertensive, and had lower type A behavior scores (Table 1).

Table 1: Baseline Characteristics by Mortality Status (N=495)

Covariate	Deceased (n=125)	Alive (n=370)	p-value
Age (years)	33.4 (6.3)	27.7 (6.4)	<0.0001
Duration	24.4 (6.5)	18.8 (6.8)	<0.0001
Percent Males (n)	53.6 (67)	47.0 (174)	0.19
Education %(n), Above High School	60.0 (75)	65.9 (244)	0.22
HbA1c (%)	9.1 (1.6)	8.6 (1.4)	<0.01
Insulin Dose (Total units/kg body weight)	0.73 (0.29)	0.76 (0.21)	0.25
Glucose Testing at Least Once per Week, %(n), Yes	64.0 (80)	63.7 (236)	0.96
WBC	7.4 (2.0)	6.2 (1.7)	<0.0001
Total caloric expenditure in sports /week (kilocalories)	0 (0.0, 525.0)	387.5 (0.0, 1440.0)	<0.0001
WHR	0.86 (0.80, 0.92)	0.82 (0.76, 0.86)	<0.0001
Fibrinogen (mg/dL)	310.0 (270.0, 390.0)	265.0 (210.0, 310.0)	<0.0001
HDL (mg/dL)	49.1 (42.5, 57.9)	53.4 (45.7, 61.8)	<0.01
non-HDL (mg/dL)	163.6 (46.7)	132.4 (38.2)	<0.0001

Table 1 Continued

Daily Calories Consumed	1895.2 (1501.5, 2441.8)	1960.5 (1528.2, 2424.2)	0.47
Ever Smoker % (n), Yes	56.8 (71)	33.7 (125)	<0.0001
Pack years of smoking (n=192)	36.5 (24.8, 48.6)	52.1 (30.4, 91.2)	<0.01
Depressive Symptomatology	8.0 (4.0, 14.0)	5.0 (2.0, 10.0)	<0.0001
Hypertension % (n), Yes	53.6 (67)	25.1 (93)	<0.0001
Lipid Medication % (n), Yes	0.80 (1)	0.54 (2)	0.74
Type A Behavior	187.2 (26.9)	194.4 (25.1)	<0.01

In combined analyses of men and women, age, sex, and education (all $p < 0.10$) were included from the demographic model between Bortner score and mortality; total sports energy expenditure and ever smoked (both $p \leq 0.05$) were included from the behavioral model; none were included from the diabetes care model (both $p > 0.10$); hypertension, non-HDL, WBC, fibrinogen, WHR, and HbA1c (all $p < 0.05$) were included from the physiological risk factor model; and BDI ($p < 0.001$) from the depressive symptomatology model. Type A behavior (Figure 2), was univariately significant in predicting mortality [HR=0.76 (0.63-0.91); $p < 0.01$].

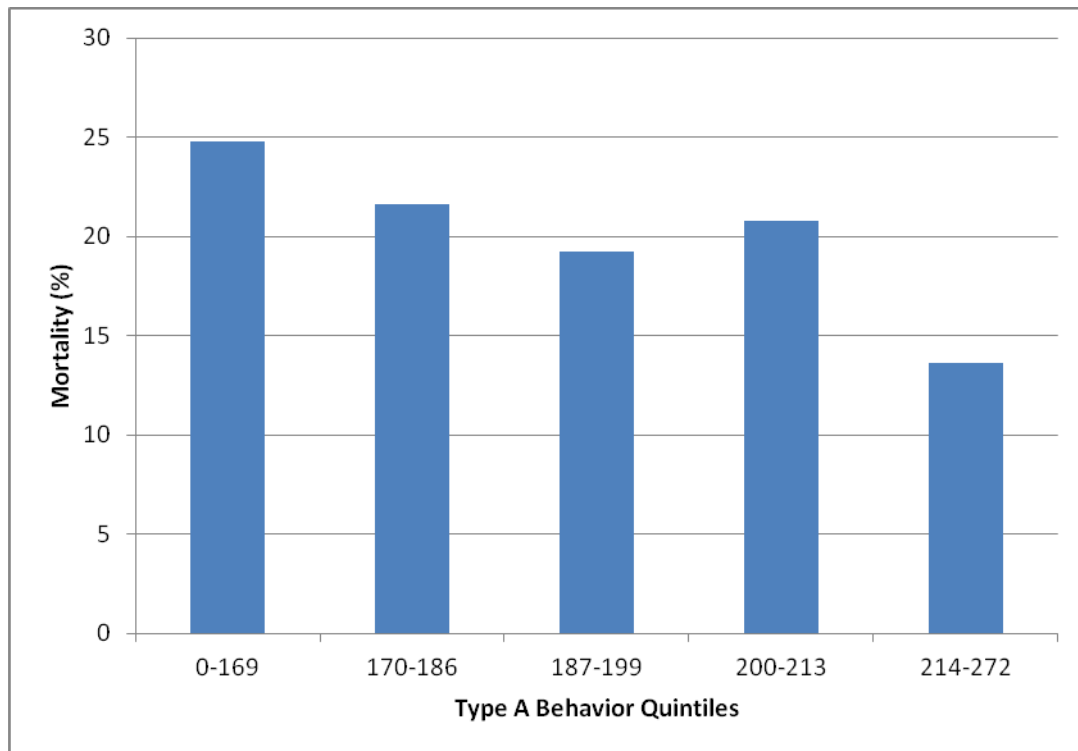


Figure 2: Type A Behavior Quintiles and Mortality; p-trend=0.01

In the final multivariable model to assess mediation, which was comprised of Bortner score and all significant covariates described above (Table 1), the association between Bortner score and mortality was no longer significant [HR= 0.94 (0.78, 1.15); p=0.58]. The individual effects of these influential covariates from each of the five risk factor models on the type A behavior and mortality relationship can be seen in Table 2.

Table 2: Individual Relationship between Type A Behavior, Influential Covariates, and Mortality (N=495)

Main Predictor	Model	Hazard Ratio	Confidence Interval	p-value
Type A Behavior [†]		0.85	(0.70-1.02)	0.08
	+ Age	1.10	(1.07-1.13)	<0.001
Type A Behavior [†]		0.81	(0.68-0.97)	0.02
	+ Fibrinogen [†]	1.55	(1.35-1.78)	<0.001
Type A Behavior [†]		0.80	(0.67-0.96)	0.01
	+ WBC	1.24	(1.16-1.34)	<0.001
Type A Behavior [†]		0.76	(0.64-0.92)	<0.01
	+ Non-HDL	1.01	(1.01-1.01)	<0.001
Type A Behavior [†]		0.77	(0.64-0.92)	<0.01
	+Beck	1.05	(1.03-1.08)	<0.001

[†] per 1 SD

The significant risk factors that appeared to explain most of the relationship between Bortner score and mortality was younger age, which increased the HR from 0.76 to 0.85 (p=0.08); non-HDL, fibrinogen, and WBC had further but less striking effects on the HR (Table 2).

Further analyses were carried out in order to examine the role of age, non-HDL, fibrinogen, and WBC and to determine if they were mediating, moderating, or confounding the relationship. Because all four (age, non-HDL, fibrinogen, and WBC) significantly predicted mortality and were also significantly associated with Bortner score (Table 3-4) we determined that, based on these two criteria and the assessment of biological plausibility, mediation may be present.

Table 3: Association between type A behavior and all-cause mortality in T1D- Stepwise Cox regression (n=495; 125 events)

Model	1	2	3	4	5	6	7	8	9	10	11
Type A Behavior	0.76 (0.63-0.91); p<0.01	0.85 (0.70-1.02); p=0.08	0.84 (0.70-1.01); p=0.07	0.87 (0.72-1.05); p=0.15	0.90 (0.74-1.09); p=0.29	0.94 (0.78-1.14); p=0.57	0.92 (0.76-1.12); p=0.44	0.91 (0.75-1.11); p=0.38	0.92 (0.76-1.12); p=0.45	0.92 (0.76-1.12); p=0.43	0.94 (0.78-1.15); p=0.58
Age		1.10 (1.07-1.13); p<0.001	1.10 (1.07-1.13); p<0.001	1.09 (1.07-1.12); p<0.001	1.09 (1.06-1.12); p<0.001	1.09 (1.06-1.11); p<0.001	1.08 (1.06-1.11); p<0.001	1.09 (1.06-1.11); p<0.001	1.09 (1.06-1.11); p<0.001	1.08 (1.05-1.11); p<0.001	1.08 (1.05-1.11); p<0.001
Sex			0.73 (0.51-1.03); p=0.08	0.85 (0.60-1.22); p=0.39	0.77 (0.54-1.11); p=0.17	1.47 (0.91-2.38); p=0.10	1.30 (0.81-2.10); p=0.27	1.38 (0.85-2.25); p=0.18	1.49 (0.91-2.46); p=0.11	1.75 (1.05-2.92); p=0.03	1.59 (0.95-2.68); p=0.07
non-HDL				1.01 (1.00-1.01); p<0.001	1.01 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.01	1.00 (1.00-1.00); p=0.01	1.00 (1.00-1.01); p=0.07
Fibrinogen*					1.41 (1.20-1.66); p<0.001	1.38 (1.18-1.61); p<0.001	1.34 (1.15-1.57); p<0.001	1.26 (1.08-1.48); p<0.01	1.23 (1.05-1.44); p<0.01	1.20 (1.02-1.41); p=0.02	1.20 (1.01-1.42); p=0.02
WHR*						1.62 (1.27-2.03); p<0.001	1.55 (1.22-1.96); p<0.001	1.58 (1.23-2.02); p<0.001	1.61 (1.25-2.08); p<0.001	1.62 (1.26-2.09); p<0.001	1.54 (1.19-2.00); p<0.001
Depressive Symptomatology							1.03 (1.01-1.06); p<0.01	1.04 (1.01-1.06); p<0.01	1.03 (1.01-1.06); p<0.01	1.04 (1.01-1.06); p<0.01	1.04 (1.01-1.06); p<0.01
HbA1c								1.20 (1.06-1.36); p<0.01	1.23 (1.08-1.39); p<0.01	1.26 (1.11-1.42); p<0.001	1.26 (1.11-1.44); p<0.001
Ever smoker									1.62 (1.12-2.35); p<0.01	1.83 (1.25-2.66); p<0.01	1.66 (1.12-2.45); p=0.01
Hypertension										1.85 (1.25-2.74); p<0.01	1.92 (1.30-2.84); p<0.01
WBC											1.10 (1.00-1.20); p=0.03

^aFinal Model= allowed for age, sex, duration, education, calories consumed, total sports, smoking, insulin dose, testing per week, hypertension, HDL, non-HDL, lipid medication, WBC, fibrinogen, WHR, HbA1c, and depressive symptomatology

Table 4: Correlations between Type A Behavior and the Covariates

Covariate	Type A Behavior	Mean Bortner by Categorical Covariates	
Age (years)	-0.197***	--	--
Duration	-0.149***	--	--
HbA1c (%)	0.043	--	--
Insulin Dose (Total units/kg body weight)	0.023	--	--
WBC	-0.116**	--	--
Total caloric expenditure in sports /week (kilocalories)	0.149***	--	--
WHR	-0.096*	--	--
Fibrinogen (mg/dL)	-0.120*	--	--
HDL (mg/dL)	0.077	--	--
non-HDL (mg/dL)	-0.091*	--	--
Daily Calories Consumed	0.103*	--	--
Depressive Symptomatology	-0.040	--	--
Ever Smoker	--	No 195.4 (25.9)**	Yes 188.1 (24.9)**
Hypertension	--	No 193.6 (25.4)	Yes 190.2 (26.4)
Lipid Medication	--	No 192.6 (25.8)	Yes 183.3 (13.2)
Sex	--	Male 193.7 (26.6)	Female 191.4 (24.9)
Education	--	Above High School 195.8 (25.3)***	Below High School 186.6 (25.6)***
Glucose Testing at Least Once per Week	--	No 194.3 (26.3)	Yes 191.6 (25.4)

*p<0.05

**p<0.01

***p<0.001

To assess whether they were full or partial mediators, each was placed separately in a Cox proportional hazards model along with Bortner score to determine if age, non-HDL, fibrinogen, or WBC would cause the HR between Bortner score and mortality to reach HR=1.0. Because none of the three totally eliminated the relationship between Bortner score and mortality, we determined that while none of these variables were full mediators, some might be partial mediators.

Before concluding these were mediators, we tested for an interaction between each of the three variables and Bortner score in predicting mortality to determine if moderation was present. Fibrinogen had a borderline significant ($p=0.06$) interaction while non-HDL and WBC did not, though this may be due to our sample size. Age did not significantly interact with Bortner score in the prediction of mortality, and because it is not plausible for age to be a mediator, it is most likely operating as an antecedent modifier. Therefore, we concluded that fibrinogen was a moderator while non-HDL and WBC had the potential to be mediators. Lastly, we tested for an interaction between Bortner score and BDI and found a $p\text{-value}=0.18$. Because depressive symptomatology is also predictive of mortality but is unlikely to be directly caused by type A behavior, it is possible that depressive symptomatology is a confounder in this relationship. Based on the analyses, the definitions used to define mediators, moderators, and confounders, and biological plausibility, we determined that depressive symptomatology was a confounder, non-HDL and WBC were mediators, fibrinogen was a moderator, and age was an antecedent modifier (Figure 3).

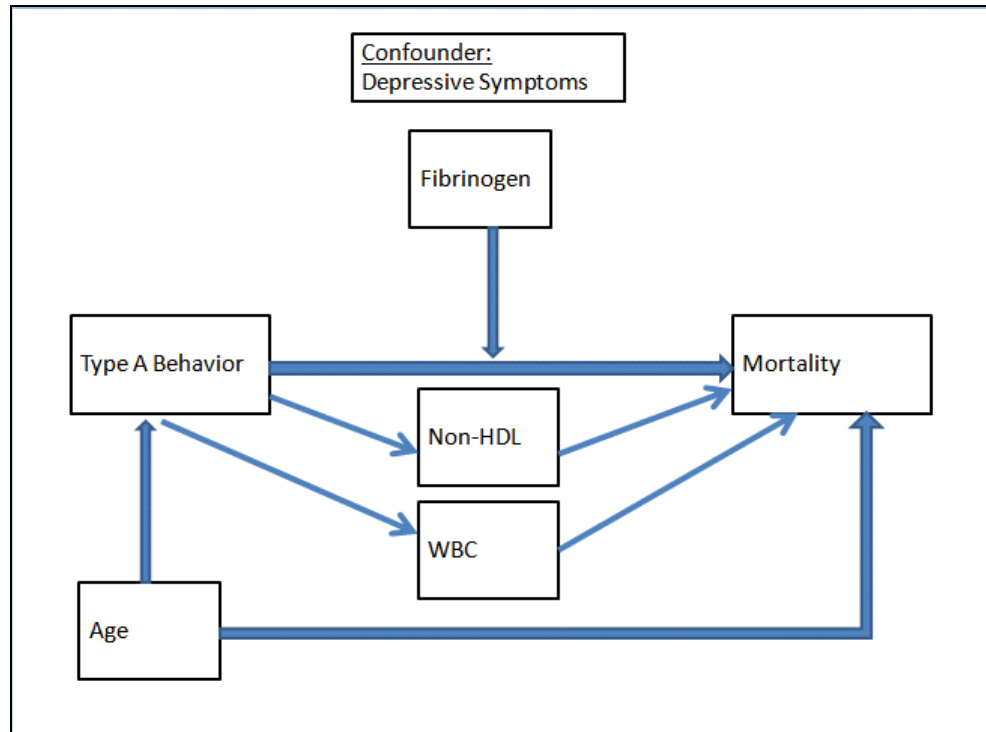


Figure 3: Mediators, Moderators, and Confounders for Combined Men and Women (n=495)

Because of prior sex variations in the role of psychosocial factors, similar sex specific analyses were conducted although the Bortner-gender interaction was non-significant ($p=0.28$) [140]. There was a significant univariate association between Bortner score and mortality found in men [$HR=0.68$ ($0.53, 0.87$); $p<0.01$] but not in women [$HR=0.84$ ($0.65-1.09$); $p=0.20$]. The association between Bortner score and mortality in men was lost in the multivariable analysis [$HR=0.87$ ($0.65-1.16$); $p=0.36$] (Table 5). Most of the factors that appeared to explain the relationship between Bortner score and mortality in men were the same as in the combined analyses, with the addition of WHR (HR increased from 0.81 to 0.84; $p=0.22$) and calories consumed (HR increased from 0.81 to 0.86; $p=0.30$) (Table 5) (Figure 4).

Table 5: Association between type A behavior and all-cause mortality in T1D in men- Stepwise Cox regression (n=241; 67 events)

Model	1	2	3	4	5	6	7	8	9	10	11
Type A Behavior	0.68 (0.53-0.87); p<0.01	0.78 (0.61-0.99); p=0.04	0.81 (0.63-1.05); p=0.12	0.84 (0.65-1.10); p=0.22	0.82 (0.63-1.08); p=0.17	0.81 (0.62-1.07); p=0.14	0.86 (0.65-1.14); p=0.30	0.86 (0.65-1.15); p=0.32	0.91 (0.68-1.21); p=0.52	0.88 (0.66-1.17); p=0.40	0.87 (0.65-1.16); p=0.36
Age		1.10 (1.06-1.14); p<0.001	1.09 (1.05-1.13); p<0.001	1.06 (1.01-1.10); p<0.01	1.06 (1.01-1.10); p<0.01	1.06 (1.01-1.10); p<0.01	1.06 (1.02-1.10); p<0.001	1.06 (1.02-1.10); p<0.001	1.06 (1.02-1.10); p<0.001	1.05 (1.02-1.09); p<0.01	1.05 (1.01-1.09); p=0.01
non-HDL			1.01 (1.00-1.01); p<0.001	1.01 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p=0.01	1.00 (1.00-1.01); p=0.01	1.00 (1.00-1.01); p=0.01	1.01 (1.00-1.01); p=0.02	1.01 (1.00-1.01); p=0.08	1.01 (1.00-1.01); p=0.08
WHR*				1.97 (1.41-2.74); p<0.001	1.85 (1.34-2.55); p<0.001	1.92 (1.37-2.71); p<0.001	2.00 (1.42-2.82); p<0.001	2.03 (1.43-2.88); p<0.001	1.96 (1.38-2.77); p<0.001	1.89 (1.34-2.68); p<0.001	2.02 (1.40-2.92); p<0.001
Fibrinogen*					1.36 (1.10-1.68); p<0.001	1.27 (1.01-1.58); p=0.03	1.22 (0.97-1.52); p=0.08	1.11 (0.87-1.41); p=0.37	1.08 (0.84-1.38); p=0.53	1.09 (0.85-1.40); p=0.45	1.05 (0.82-1.35); p=0.66
HbA1c						1.21 (1.00-1.46); p=0.04	1.21 (1.01-1.46); p=0.03	1.23 (1.02-1.49); p=0.02	1.27 (1.05-1.54); p=0.01	1.28 (1.06-1.55); p<0.01	1.31 (1.08-1.59); p<0.001
Calories Consumed							1.00 (0.99-1.00); p=0.04	1.00 (0.99-1.00); p=0.02	0.99 (0.99-1.00); p=0.01	1.00 (0.99-1.00); p=0.01	0.99 (0.99-1.00); p<0.01
Depressive Symptomatology								1.03 (1.00-1.07); p=0.03	1.03 (1.00-1.07); p=0.03	1.04 (1.00-1.08); p=0.01	1.04 (1.00-1.08); p=0.02
WBC									1.14 (1.00-1.30); p=0.04	1.16 (1.01-1.32); p=0.02	1.12 (0.97-1.28); p=0.09
Hypertension										1.74 (1.00-3.04); p=0.04	2.01 (1.14-3.57); p=0.01
Ever Smoker											1.69 (0.97-2.96); p=0.06

^aFinal Model= allowed for age, duration, education, calories consumed, total sports, smoking, insulin dose, testing per week, hypertension, HDL, non-HDL, lipid medication, WBC, fibrinogen, WHR, HbA1c, and depressive symptomatology

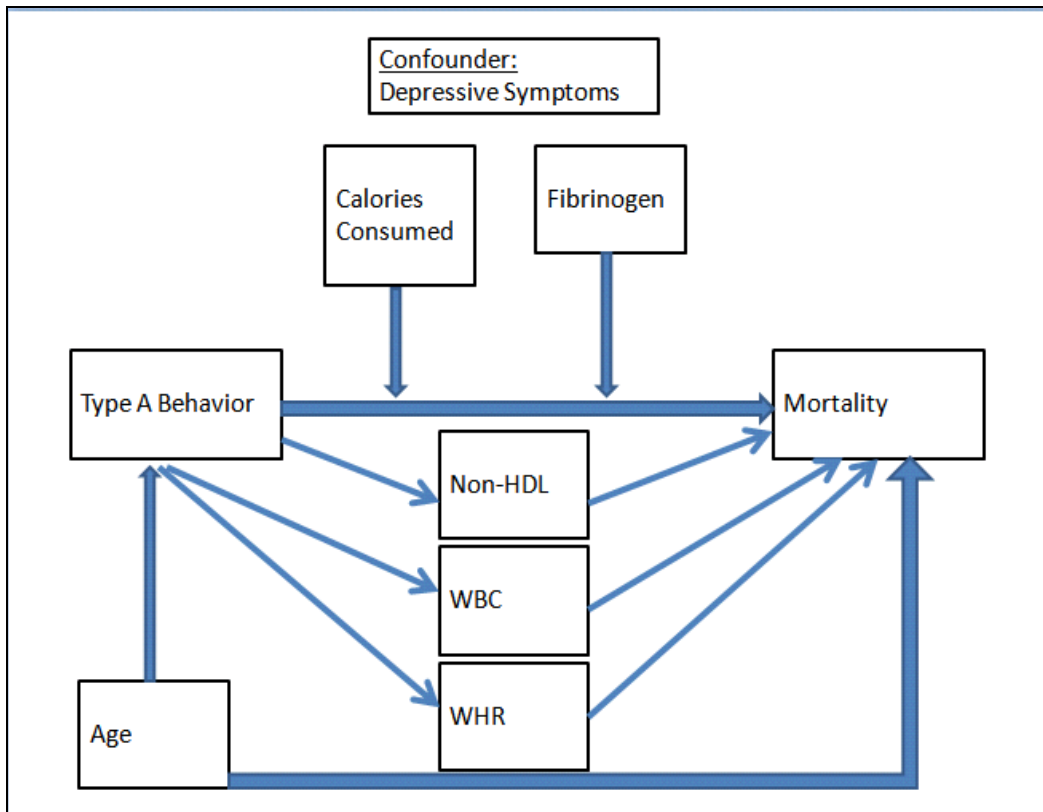


Figure 4: Mediators, Moderators, and Confounders for Men Only (n=241)

Next, to better understand the role of these additional influential covariates, we investigated whether these variables were mediators, moderators, or confounders in the Bortner score and mortality relationship. We found that WHR did not significantly interact with Bortner score ($p=0.22$) while calories consumed did ($p=0.05$). Thus, we concluded that WHR was a likely mediator and calories consumed were a moderator in the relationship between Bortner score and mortality.

Based on our previously published work where we found a significant interaction between Bortner score and BDI so that Bortner score was only operative in those with a low BDI [83], we tested for an interaction between Bortner score and BDI in men and now found the interaction term to be non-significant in predicting mortality ($p=0.17$). Because in our

previously published work the Bortner score and depressive symptomatology interaction was more significant in men, we repeated these findings in our current population and found that in those with a BDI<7 (prior median cut-point used), total Bortner score was more protective against mortality ($p=0.16$) compared to in those with a BDI score of ≥ 7 , where Bortner score lost most of its protective effect ($p=0.47$).

2.4 DISCUSSION

In this current analysis, we have built on our previous research, which demonstrated a protective effect of type A behavior on mortality in those with T1D through further investigation of how the covariates influence the relationships between the other risk factors and mortality (confounders vs. moderators vs. mediators). Overall, we found that in men and women combined, type A behavior (as indicated by the Bortner score) was univariately protective against mortality, however this relationship was no longer significant after other risk factors were considered, due, most prominently, to the additions of age (antecedent moderator), non-HDL and WBC (mediators), and fibrinogen (moderator) (Figure 3). When these analyses were performed separately by sex, type A behavior was univariately protective against mortality in men but not in women. However, in men this relationship was lost in the multivariable modeling, most predominately after WHR (mediator) and age (antecedent moderator) were taken in to account in the type A behavior and mortality relationship (Figure 4).

It is an interesting finding that age moderates the relationship between type A behavior and mortality because it seems that behavior type may differ across the lifespan. Our findings fit in with much of the literature that suggests that personality changes with age [141]–[145]. In our

population, age (a known risk factor for mortality) was negatively correlated with type A behavior, but is not caused by type A behavior, thus leading to our conclusion that age is an antecedent moderator in the relationship between type A behavior and mortality. In other words, younger participants scored themselves higher on the Bortner scale compared to older participants. This may be due to several factors, including younger people having more energy for time urgency or they may be new in their careers and extremely motivated and energetic.

Type A behavior may be linked to mortality through a relationship with inflammation in the body. Previous investigators have found that several markers of inflammation were significantly increased in subjects with T1D compared with controls [146]. In addition, inflammation increases vascular disease, which in turn increases the risk of mortality [59]–[61], [147]–[150]. Because of this pathway, it is plausible that low type A behavior scores may lead to increased inflammation levels/stress reactants (marked by increased WBC and non-HDL) and, further moderated by fibrinogen, may increase the risk for mortality in those with T1D through complications. Furthermore, according to our results, the protection offered through type A behavior on mortality operates best among those with low levels of fibrinogen. Our analyses suggested that two markers of inflammation, WBC and non-HDL, operated as mediators while the other fibrinogen, operated as a moderator. Biological plausibility wise, this difference is difficult to explain. Fibrinogen had only a borderline significant interaction with type A behavior in mortality prediction, so perhaps it is actually working as a mediator, or we did not have enough statistical power to detect interactions with the other two and type A behavior.

It is also difficult to tease out whether those who had high type A behavior scores had a reduced risk of inflammation or if those who scored themselves low on the Bortner Scale had high levels of inflammation and possible subclinical disease leading to mortality. While the

Bortner Score most likely indicates a combination of a health status and genuine behavior, type A behavior's relationship with mortality was not completely eliminated after non-HDL and WBC mediated the relationship, after fibrinogen modified the relationship, or with age functioning as an antecedent moderator. Therefore, it seems likely that type A behavior was not simply a marker of health since the inflammatory markers did not fully explain its relationship with mortality (Table 3) and thus did represent some benefit of the behavior type, as well.

Because we found non-HDL to be a mediator between type A behavior and mortality, we looked into the literature to investigate whether other studies support this finding. A separate study comprised of older participants free from diabetes found that those with type A behavior compared to type B behavior had higher serum total cholesterol [151]. After analyses, the authors concluded that there might be an association between type A behavior and lipid metabolism, however they did not take gender and age into account while investigating this relationship which may not have properly accounted for confounding [151]. Another study found similar results in a general Cretan population: that total serum cholesterol level was positively associated with type A behavior score [152]. In our population of people T1D, non-HDL had a significant, negative correlation with type A behavior score, which is opposite of what was observed in these other populations. This is consistent with type A behavior having a protective effect in high risk populations compared to a potential detrimental effect in the general population, most likely due to people living with a chronic disease benefiting from a more regimented behavior type [70], [153], [154]. Because non-HDL was determined to be a mediator, it appears that higher type A behavior leads to a person's lower non-HDL cholesterol level and therefore reduced mortality risk.

In our sex-specific analyses, men were protected against mortality by high type A behavior before considering other variables, with lower WHR and age subsequently having the largest effect on this relationship. However, in women, type A behavior provided no protection against mortality. WHR was found to be a partial mediator, age an antecedent moderator, and depressive symptomatology appeared to confound but not moderate the relationship between type A behavior and mortality in men.

A relationship between type A behavior and WHR has previously been demonstrated in our population, particularly in men, with a higher WHR associated with lower type A behavior score [97]. Our current data fit in with this, as WHR was an important risk factor in the relationship between type A behavior and mortality, greatly reducing the protective effect of type A behavior on mortality. Again, this mediating relationship is difficult to understand. Because WHR is a mediator, it is in the causal pathway between type A behavior and mortality, therefore, it seems that those who rated themselves higher on the type A behavior questionnaire had lower WHR and therefore a reduced risk of mortality. However, having a lower WHR mediated the effect high type A behavior had on mortality risk but did not completely eliminate the demonstrated relationship. While WHR did not affect the hazard ratio as drastically in men and women combined, this is most likely due to it having a close relationship with the inflammatory markers in the combined population and thus its contribution to the mediation was diluted by the inclusion of the inflammatory markers. Based on WHR not completely eliminating the relationship in men, it seems that a combination of behavior type and traditional health markers for mortality are occurring together and Björntorp's theory regarding stress and comorbidities becomes important [155].

Björntorp theorizes that elevated cortisol may cause the accumulation of fat in visceral adipose tissues as well as cause the metabolic syndrome [155]. He further describes these relationships by noting that depression in men is followed with time by similar abnormalities. Several factors, including psychosocial and socioeconomic disadvantages and depressive symptomatology and anxiety may increase stress. It is possible that 'stress-eating' may result, increasing abdominal adiposity (measured in our cohort by WHR) [155]. This theorizing, combined with our demonstrated effect of WHR's importance in men along with depressive symptomatology as a confounder, may explain the biological plausibility of WHR mediating the relationship between type A behavior and mortality.

In related work, the Japanese Collaborative Cohort Study investigated whether psychological factors had an influence on disease processes [156]. One of their included factors was "sense of hurry," which is seemingly similar to "always rushed," a component of the type A behavior questionnaire used in our study. Researchers found that participants who scored themselves "yes" on the "sense of hurry" question had a decreased risk of mortality from all causes compared to "maybe yes" while those rating themselves as "no" had an increased risk for mortality in both sexes. They hypothesized that this relationship may be due to these participants rating themselves as "yes" and above on "sense of hurry" having a generally more positive attitude regarding their lives [156].

To expand on this idea regarding type A behavior and increased positivity, a separate, small, United States study researched whether stress-induced declines in positivity increased inflammation, and in turn, whether this increase was associated with increased depressive symptomatology in women [157]. Authors found that a decreased positive outlook during stress was associated with high pro-inflammatory reactivity and that there was a borderline trend

towards higher depressive symptomatology. Through a mediation model, they determined a significant mediation effect such that decreased positive outlook during stress lead to increased inflammation, which lead to increased depressive symptomatology. Authors conclude that these results demonstrate potential that those who maintain hope and confidence during stress may be at a reduced risk of depressive symptomatology. It seems that something similar is happening in our population. A low type A behavior score, and thus potential low positivity, may work with increased inflammation and depressive symptomatology to increase the risk for mortality.

In our study, we considered a large number of covariates as possible explanatory factors between type A behavior and mortality. Although the Japanese study saw a protective effect in both men and women, we only saw this effect in men. Their hypothesis about these participants having a positive life outlook may be applicable to our T1D population. Living with T1D poses many stresses and worries that the general population, free from a chronic disease, may not experience. Perhaps rating oneself very high on the type A behavior scale is indicative of having the enthusiasm to rush to complete daily tasks and create busy schedules for themselves despite challenges stemming from their chronic disease. This enthusiasm seems like it would be a marker of an overall positive attitude. The second study described above demonstrated that an increased positive outlook during a stressor may protect against inflammation in the body, as well as against depressive symptomatology which we have demonstrated to be an increased risk factor for mortality [100]. Those with type A behavior in our study may have a more positive outlook in general, offering protective benefits against mortality.

A limitation of our study was the number of participants excluded from the analyses as well as the excluded participants being sicker than those included. However, we described the differences in populations and confirmed that those excluded were not significantly different

regarding their type A behavior scores. In our current study, age influenced the relationship between type A behavior and mortality to a larger degree than our previous work. This difference is most likely due to the difference in populations (20 discordant participants) resulting from the use of different covariates. The purpose of the current study was to understand the type A behavior and mortality relationship in greater detail, thus a more extensive list of covariates was utilized.

Future research should focus on continuing to understand the benefit type A behavior has on delaying mortality and how it interacts with other potentially important psychosocial factors (e.g. social support, hostility, stress, anger, and anxiety mechanisms). In conclusion, we were able to derive a better understanding of the type A behavior association with mortality using these select components as well as analyses to determine whether mediation, moderation, or confounding was present using several levels of risk factors. We conclude that there may be protective aspects of high type A behavior that play an important role in mortality prevention, but that age, WHR, non-HDL, and inflammatory markers can largely explain this protection. We hope future research will be able to use these psychosocial findings to delay mortality in people with T1D.

3.0 PSYCHOSOCIAL FACTORS AND THEIR INTERACTIONS IN THE PREDICTION OF MORTALITY

We expanded on our previous research by examining a complete list of covariates in the type A behavior and mortality relationship. In addition, we have also previously demonstrated a relationship between depressive symptomatology and mortality. As discussed above, there is a substantial gap in the literature in terms of studying how psychosocial factors interact with one another to predict mortality. Thus, we examined whether psychosocial risk factors interact with type A behavior and depressive symptomatology to predict mortality up to 22-years later in our T1D population.

3.1 INTRODUCTION

Psychosocial factors, including depressive symptomatology, type A behavior, hostility, trait-anger, anxiety, and social support, have all been associated with health outcomes in the general population and somewhat within those with T1D. T1D is mostly diagnosed in children and young adults, although it can occur at any age [2]. The EURODIAB study, which involves a registry of 44 countries in Europe, suggests an annual rate of increase of 3-4% in incidence of T1D. Although survival in those with T1D has improved [4]–[12], [15], the population continues to be at an increased risk of several long-term complications [129]. While several modifiable risk

factors are recognized for the development of these complications, how psychosocial factors may interact to contribute to early mortality in people with T1D is understudied.

It has been previously demonstrated that higher depressive symptomatology is associated with increased mortality [91] and morbidity risk (including diabetes complications) [92]. Co-morbid depression and T1D is also associated with poorer diabetes self-management and metabolic control, decreased quality of life, and higher healthcare usage [91]. In addition, one study found that those with T1D were over three and a half times more likely to have depression, over two and a half times more likely to have a history of depression, and were twice as likely to be on an antidepressant than people free from T1D [93]. Through a meta-analysis, investigators found a prevalence of depression between 12.0% and 13.4% in T1D [158].

Personality type and behavioral factors have also been found to be associated with health outcomes. People characterized as having type A behavior tend to focus on accomplishing more in less time than others, and are often more competitive, time urgent, and work-oriented [70]. We have previously demonstrated that those with T1D and higher type A behavior scores interact with depressive symptomatology such that those with high type A behavior have lower all-cause mortality in the absence of high depressive symptomatology [83]. In addition, cross-sectional analysis has shown type A behavior to be negatively associated with the number of complications present in those with T1D [72]. The authors hypothesized that this may be due to a protective effect of some aspect of behavior regarding self-management of diabetes leading to a reduced risk of complication development [72]. A combination of depressive symptomatology, type A behavior, and other psychosocial factors may improve the prediction of mortality compared to studying them separately.

A potentially detrimental psychosocial factor is hostility, and a recent meta-analysis found, via their subgroup analyses, that the Minnesota Multiphasic Personality Inventory (MMPI) and its derivative, the Cook-Medley hostility scale (CMHS) were significantly associated with CHD events in healthy and existing CHD study cohorts, with increased hostility resulting in an approximate 20% increase in CHD event risk in both populations [102]. Another study conducted in a population of African-Americans with T1D found that the development of hypertension over a 6-year follow-up period was independently predicted by hostility and overt proteinuria [105].

Anger, which is usually examined in combination with hostility but exists as its own construct, is an additional psychosocial area of focus in the literature. Anger can be described as “an emotional state that consists of feelings that vary in intensity from mild irritation or annoyance to intense fury or rage, and aggressiveness as a verbal or physical behavioral pattern manifest in yelling, intimidation, or physical assaults [102].” The limited literature that exists suggests that anger is associated with increased CHD events in healthy population studies as well as in those with existing CHD [102]. The literature surrounding T1D and hostility and trait-anger is, however, extremely limited.

An additional important psychosocial factor in chronic disease progression is anxiety, with anxiety-related personality traits found to be associated with increased risk for the development of depression and anxiety-related disorders [159]. As expected, anxiety is more prevalent in the diabetes population than in the general population partially due to the burden of living with a chronic disease [114]. A study found that generalized anxiety disorder was prevalent in about 5% of their population [113]; investigators also found that within their

participants with stable CAD, anxiety and depression resulted in increased odds of having a cardiac event over two years of follow-up, even after multivariable adjustments [113].

An additional psychosocial factor, social support, has also been found to influence health [125], [126], [160], [161]. Social support refers to the network of family and friends surrounding a person in their external environment. A review concluded that peer support demonstrated some potential to improve diabetes related outcomes; however, the existing evidence is too inconsistent and sparse to maintain an overall consensus [126]. A separate clinical trial of people with diabetes, through the Veteran's Affairs Organization, [161] demonstrated that reciprocal peer support resulted in a significant decrease in HbA1c level six months later compared to the usual care group, where HbA1c levels actually increased. They also found that the reciprocal peer support group reported greater increases in social support at six months compared to the usual care group, thus demonstrating a change in perceived social support, as well [161].

In summary, depressive symptomatology, type A behavior, hostility, trait-anger, anxiety, and social support have all been associated with health outcomes in the general population and in those with diabetes. In T1D, we have previously demonstrated that depressive symptomatology is an independent predictor of mortality in both men and women [100], as is type A behavior [83]. A recurring theme within the literature is the potential web these factors form with one another and how different combinations and interactions may affect health outcomes [132], [137]. We thus examined whether the psychosocial risk factors discussed above (hostility, trait-anger, anxiety, stress, and social support) interacted with type A behavior and depressive symptomatology to predict mortality in our T1D population over a 22-year follow-up period.

3.2 METHODS

The EDC Study is comprised of T1D participants diagnosed between 1950 and 1980 at age <17 years. These participants were seen within one year of diagnosis at the Children's Hospital of Pittsburgh. Biennial follow-up has occurred since baseline (1986-1988) with surveys and, for the first 10 years and again at 18 years, with examinations. These follow-ups included questionnaires, physician examinations, and laboratory analyses of urine and blood. Data up to the 22-year follow-up are now available.

Participants ≥ 18 years of age at study entry completed a series of forms including the Bortner Rating Scale, the Interpersonal Support Evaluation List, the Spielberger Anger/Anxiety Scale, the Cook-Medley Hostility Scale, Cohen's Perceived Stress Scale, and the BDI, which were examined in the analyses. The BDI is a 21-item self-report scale that is widely used in both healthy and ill populations to measure depressive symptomatology [137]. The Bortner Rating Scale measures aspects of type A behavior, and participants circled where they fell on the dotted line between items like "always rushed" and "never rushed, even under pressure" (Appendix A) [132]. A slightly modified (with wording changed on item 2) version of the 10 statement Appraisal Scale component of The Interpersonal Support Evaluation List [162] was used and measures the perceived accessibility of someone with which to talk about one's problems. The Spielberger Trait Anger-Anxiety Scale [163] was used to measure trait (how people generally feel during typical situations experienced on a regular basis) anger and anxiety. The Cook-Medley Hostility Scale was utilized [164], which measures various cognitive, emotional, and behavioral characteristics of someone's negative orientation towards interactions with others [164]. Lastly, Cohen's 5 item Perceived Stress Scale [165] was used to measure perceived level of stress during the past month.

Overall mortality and complication status was determined as of February 25, 2011. The underlying causes of death, and the hierarchical order for all contributing causes of death, were determined by a Mortality Classification Committee consisting of two or more physician epidemiologists [166]. Covariates were chosen based on prior evidence for our final mortality prediction models [83], [133]. Education was assessed using a 5-point scale, and then dichotomized to above or below a high school education. Daily calories consumed were measured through use of the Willett Food Frequency Questionnaire averaged over a week [167]. Physical activity was assessed using questions about current levels of leisure activities [168]. Smoking status was defined by whether or not more than 100 cigarettes had been smoked over their lifetime. Insulin dosage was expressed as the number of units of insulin used per day divided by the participants' weight in kilograms. Frequency of blood glucose testing per week was reported as the number of times blood glucose levels were tested each week.

Hypertension was defined as systolic blood pressure $SBP \geq 130$ or $DBP \geq 80$ or on blood pressure medication. Fasting blood samples were assayed for lipids, WBC count, and fibrinogen as previously described [136], [169]. Fasting blood samples were also analyzed for HbA1 (microcolumn cation exchange; Isolab, Akron, OH, USA), and these original HbA1 values were converted to DCCT-aligned HbA1c for all analyses using a regression equation derived from duplicate assays ($DCCT\ HbA1c = 0.14 + 0.83[EDC\ HbA1]$). WHR ratio was calculated by measuring at the smallest circumference of the natural waist and then measuring the hip circumference at the widest part of the buttocks or hip.

Cox proportional hazards models were utilized to examine the univariate relationship between baseline type A behavior (Bortner Score) and mortality, depressive symptomatology (BDI score) and mortality, and other baseline covariates and mortality. Student's t-tests or

Wilcoxon rank-sign tests were used to assess the univariate associations between the primary predictors of interest, Bortner Score and BDI, and other covariates, including trait-anger. Cox proportional hazards modeling was then used to examine the multivariable relationship between Bortner Score, controlling for significant baseline covariates, and overall mortality over 22 years of follow-up. The same was repeated with BDI as the main predictor.

A correlation matrix of the psychosocial variables (main predictors: type A behavior and depressive symptomatology; covariates: trait-anger, anxiety, hostility, support, and stress) was completed, and when significant correlations between the psychosocial variables ≥ 0.65 , residual values were calculated by regressing the correlated psychosocial variables on one another. These calculated residual values were then used in the multivariable models in place of the original psychosocial variables. This allowed us to assess the impact of each psychosocial variable independent of the other, correlated variables. BDI was highly correlated with anxiety and stress, so we regressed anxiety and stress on to BDI to calculate a residual value and used that value in the model in place of the original BDI value for each observation. We regressed BDI and stress on to anxiety to calculate a residual value for anxiety, and used it as described for BDI. Lastly, we regressed BDI and anxiety on to stress to calculate a residual value for stress, and again, used it the same way in our modelling. Interactions between Bortner Score and BDI and the other psychosocial variables were evaluated and used in multivariable modeling as appropriate. All statistics were performed using SAS 9.3 (SAS Institute, Cary, NC).

3.3 RESULTS

At the baseline visit, 592 participants were 18 years and older and eligible to complete the psychosocial questionnaires. One hundred participants were excluded from this analysis for having missing covariate measures, primarily the psychosocial questionnaires and physical activity measures. Out of those who were age eligible, those who were excluded had a higher WBC count, a higher WHR, were more likely to be male, ever smokers, and were less likely to have higher than a high school education.

Out of the remaining 492 participants, there were 125 deaths (25.4%). As expected, differences existed by subsequent mortality for most baseline covariates. Deceased participants tended to be older, with longer diabetes duration, higher HbA1c, higher insulin dose, higher WBC, lower physical activity levels, higher WHR, fibrinogen, non-HDL, lower HDL, were more likely to be smokers, have hypertension, higher BDI scores, lower interpersonal support, and lower Bortner Scale scores (Table 6).

Table 6: Baseline Characteristics by Mortality Status (N= 492)

Covariate	Deceased (n=125)	Alive (n=370)	p-value
Age (years)	33.4 (6.3)	27.6 (6.5)	<0.0001
Duration	24.4 (6.5)	18.7 (6.8)	<0.0001
Percent Males %(n)	53.8 (63)	46.8 (177)	0.18
Education %(n), Above High School	58.9(69)	65.6 (248)	0.19
HbA1c (%)	9.1 (1.6)	8.6 (1.4)	<0.01
Insulin Dose (Total units/kg body weight)	0.65 (0.53, 0.85)	0.75 (0.62, 0.88)	<0.01

Table 6 Continued

Glucose Testing at Least Once per Week, %(n), Yes	64.0 (80)	63.7 (234)	0.96
WBC	7.0 (6.0, 8.8)	6.0 (5.1, 7.2))	<0.0001
Total caloric expenditure in sports /week (kilocalories)	0 (0.0, 525.0)	387.5 (0.0, 1425.0)	<0.0001
WHR	0.86 (0.80, 0.92)	0.82 (0.76, 0.86)	<0.0001
Fibrinogen (mg/dL)	310.0 (270.0, 390.0)	270.0 (210.0, 310.0)	<0.0001
HDL (mg/dL)	49.1 (42.5, 57.9)	53.4 (45.8, 61.4)	<0.01
non-HDL (mg/dL)	159.2 (133.0, 187.6)	125.2 (104.4, 150.8)	<0.0001
Daily Calories Consumed	1895.2 (1501.5, 2441.8)	1958.2 (1528.2, 2419.9)	0.50
Ever Smoker % (n), Yes	56.4 (66)	34.1 (129)	<0.0001
Hypertension % (n), Yes	55.5 (65)	24.8 (94)	<0.0001
Lipid Medication % (n), Yes	0.85 (1)	0.53 (2)	0.69
Hostility	98.0 (12.6)	98.1 (11.9)	0.96
Anger	20.0 (16.0, 23.0)	19.0 (16.0, 23.0)	0.29
Anxiety	19.0 (15.0, 24.0)	19.0 (15.0, 24.0)	0.88
Depressive Symptomatology	8.0 (4.0, 14.0)	5.0 (2.0, 10.0)	<0.0001
Stress	12.0 (11.0, 16.0)	13.0 (11.0, 16.0)	0.59
Interpersonal Support-Appraisal Scale	7.0 (5.0, 9.0)	8.0 (6.0, 9.0)	0.05
Type A Behavior	187.2 (26.9)	194.4 (25.2)	<0.01

Residual values for BDI scores, anxiety, and stress (as described above) were used in modeling and in interaction assessment as these three variables were highly correlated. Residual

BDI scores [HR=1.65 (1.41-1.934); $p<0.0001$] and Bortner Scale scores [HR=0.76 (0.63-0.91); $p<0.01$] were univariately associated with mortality. We tested for interactions between residual BDI scores and Bortner Scale scores and the other psychosocial covariates, and found that residual BDI scores had a borderline interaction only with trait-anger ($p=0.08$) while Bortner Score did not significantly interact with any of the psychosocial variables. Interaction terms were used as predictors where appropriate ($p<0.10$) in the two separate multivariable models: one for residual BDI scores and mortality and one for Bortner scores and mortality. We used a step-wise approach offering age or duration, and sex first, then additional behavioral and biological risk factors, followed by psychosocial variables, and finally interactions between the psychosocial variables if applicable (Tables 7-8).

Table 7: Final Multivariable Models of depressive symptomatology and all-cause mortality in T1D- Stepwise Cox regression (n=492; 125 events)

	1	2	3	4	5	6	7	8	9	10	11
Depressive Symptomatology	1.65 (1.41-1.93); p<0.001	1.55 (1.31-1.84); p<0.001	1.58 (1.33-1.88); p<0.001	1.49 (1.26-1.76); p<0.001	1.46 (1.23-1.72); p<0.001	1.40 (1.18-1.66); p<0.001	1.43 (1.21-1.70); p<0.001	1.36 (1.15-1.62); p<0.001	1.35 (1.13-1.61); p<0.001	1.37 (1.15-1.63); p<0.001	-----
Age^a		1.09 (1.07-1.12); p<0.001	1.09 (1.07-1.12); p<0.001	1.09 (1.07-1.12); p<0.001	1.08 (1.05-1.11); p<0.001	1.08 (1.06-1.11); p<0.001	1.08 (1.05-1.11); p<0.001	1.08 (1.05-1.10); p<0.001	1.08 (1.05-1.11); p<0.001	1.08 (1.05-1.10); p<0.001	1.08 (1.05-1.10); p<0.001
Sex (Females)			0.66 (0.46-0.95); p=0.02	0.81 (0.56-0.95); p=0.25	1.55 (0.97-2.47); p=0.06	1.64 (1.01-2.64); p=0.04	1.90 (1.16-2.59); p<0.01	2.10 (1.27-3.47); p<0.01	1.90 (1.14-3.17); p=0.01	1.53 (0.88-2.65); p=0.12	1.37 (0.79-2.39); p=0.25
non-HDL^b				1.01 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.01	1.00 (1.00-1.01); p=0.05	1.00 (1.00-1.01); p=0.06	1.00 (1.00-1.01); p=0.04
WHR[†]					1.66 (1.30-2.12); p<0.001	1.71 (1.33-2.20); p<0.001	1.70 (1.33-2.19); p<0.001	1.74 (1.35-2.26); p<0.001	1.66 (1.28-2.16); p<0.001	1.66 (1.28-2.16); p<0.001	1.64 (1.26-2.13); p<0.001
HbA1c						1.21 (1.07-1.36); p<0.01	1.22 (1.08-1.38); p<0.01	1.27 (1.12-1.44); p<0.001	1.27 (1.13-1.44); p<0.001	1.28 (1.13-1.45); p<0.001	1.28 (1.13-1.45); p<0.001
Hypertension							1.75 (1.19-2.59); p<0.01	1.94 (1.31-2.87); p<0.001	2.03 (1.37-3.00); p<0.001	2.03 (1.37-3.00); p<0.001	1.93 (1.30-2.86); p<0.01
Ever smoker								1.81(1.24-2.64); p<0.01	1.66 (1.12-2.45); p=0.01	1.69 (1.15-2.49); p<0.01	1.72 (1.16-2.55); p<0.01
WBC									1.09 (1.00-1.19); p=0.03	1.10 (1.01-1.20); p=0.02	1.10 (1.01-1.21); p=0.02
Calories Consumed										1.00 (0.99-1.00); p=0.04	1.00 (0.99-1.00); p=0.04

Table 7 Continued

Depressive SymptomatologyxAnger ^d											p=0.09
AIC:	1462.2	1411.6	1408.7	1377.8	1364.0	1356.2	1350.6	1342.9	1340.6	1338.5	1336.8

*Residual Value

[†]Accompanying HR (95% CI) per 1 SD change in item score

Model^a allowed for: age, sex

Model^b allowed for: age, sex, duration, education, calories consumed, total sports, smoking, insulin dose, testing per week, hypertension, HDL, non-HDL, lipid medication, WBC, fibrinogen, WHR, and HbA1c

Model^{c-d} allowed for: age, sex, duration, education, calories consumed, total sports, smoking, insulin dose, testing per week, hypertension, HDL, non-HDL, lipid medication, WBC, fibrinogen, WHR, HbA1c, anxiety, hostility, stress, and interpersonal support

Table 8: Final Multivariable Model of type A behavior and all-cause mortality in T1D- Stepwise Cox regression (n=492; 125 events)

	1	2	3	4	5	6	7	8	9	10	11
Type A Behavior	0.76 (0.63- 0.91); p<0.01	0.85 (0.70- 1.02); p=0.08	0.84 (0.70- 1.01); p=0.07	0.87 (0.72- 1.05); p=0.15	0.90 (0.74- 1.09); p=0.29	0.94 (0.78- 1.14); p=0.07	0.94 (0.78- 1.13); p=0.54	0.95 (0.79- 1.15); p=0.64	0.95 (0.79- 1.15); p=0.65	0.97 (0.80- 1.17); p=0.78	0.93 (0.77- 1.12); p=0.47
Age^a		1.10 (1.07- 1.13); p<0.001	1.10 (1.07- 1.13); p<0.001	1.09 (1.07- 1.12); p<0.001	1.09 (1.06- 1.12); p<0.001	1.08 (1.06- 1.11); p<0.001	1.09 (1.06- 1.11); p<0.001	1.08 (1.06- 1.11); p<0.001	1.08 (1.06- 1.11); p<0.001	1.08 (1.05- 1.11); p<0.001	1.08 (1.05- 1.10); p<0.001
Sex (Females)			0.73 (0.51- 1.04); p=0.08	0.85 (0.59- 1.22); p=0.39	0.77 (0.53- 1.11); p=0.17	1.41 (0.88- 2.28); p=0.14	1.51 (0.93- 2.47); p=0.09	1.63 (0.99- 2.67); p=0.05	1.86 (1.12- 3.10); p=0.01	1.72 (1.03- 2.89); p=0.03	1.71 (1.02- 2.89); p=0.04
non-HDL^b				1.01 (1.00- 1.01); p<0.001	1.01 (1.00- 1.01); p<0.001	1.00 (1.00- 1.01); p<0.001	1.00 (1.00- 1.01); p<0.001	1.00 (1.00- 1.01); p<0.001	1.00 (1.00- 1.01); p=0.01	1.00 (1.00- 1.00); p=0.07	1.00 (1.00- 1.00); p=0.08
Fibrinogen[†]					1.40 (1.19- 1.64); p<0.001	1.37 (1.17- 1.60); p<0.001	1.28 (1.08- 1.50); p<0.01	1.24 (1.05- 1.45); p<0.01	1.20 (1.01- 1.41); p=0.03	1.19 (1.00- 1.42); p=0.04	1.14 (0.96- 1.36); p=0.11
WHR[†]						1.58 (1.25- 2.00); p<0.001	1.62 (1.27- 2.07); p<0.001	1.68 (1.30- 2.15); p<0.001	1.66 (1.28- 2.14); p<0.001	1.58 (1.22- 2.05); p<0.001	1.56 (1.20- 2.03); p<0.001
HbA1c							1.20 (1.06- 1.36); p<0.01	1.23 (1.08- 1.40); p<0.01	1.26 (1.11- 1.44); p<0.001	1.27 (1.11- 1.44); p<0.001	1.23 (1.08- 1.41); p<0.01
Ever smoker								1.67 (1.17- 2.43); p<0.01	1.90 (1.30- 2.76); p<0.001	1.73 (1.17- 2.55); p<0.01	1.60 (1.08- 2.38); p=0.01
Hypertension									1.75 (1.19- 2.59); p<0.01	1.85 (1.25- 2.75); p<0.01	1.96 (1.32- 2.91); p<0.001
WBC										1.09 (1.00- 1.19); p=0.04	1.08 (0.99- 1.17); p=0.07

Table 8 Continued

Depressive Symptomatology^{c*}											1.36 (1.13-1.62); p<0.001
AIC:	1488.3	1432.6	1397.1	1383.0	1369.7	1364.1	1358.1	1352.3	1349.6	1349.6	1339.8

*Residual Value

[†]Accompanying HR (95% CI) per 1 SD change in item score

Model^a allowed for: age, sex

Model^b allowed for: age, sex, duration, education, calories consumed, total sports, smoking, insulin dose, testing per week, hypertension, HDL, non-HDL, lipid medication, WBC, fibrinogen, WHR, and HbA1c

Model^c allowed for: age, sex, duration, education, calories consumed, total sports, smoking, insulin dose, testing per week, hypertension, HDL, non-HDL, lipid medication, WBC, fibrinogen, WHR, HbA1c , anxiety, hostility, stress, depressive symptomatology, and interpersonal support

After multivariable modeling, the residual BDI scores and trait-anger interaction term remained borderline predictive of mortality ($p=0.09$), along with age, sex, non-HDL, WHR, HbA1c, hypertension, ever smoker, WBC, and calories consumed (Table 7). To examine this further, we repeated the analysis of the multivariable model stratifying by trait-anger above and below the median of 19. BDI residual scores were only predictive of mortality in those with a trait-anger score <19 [HR=2.09 (1.46-2.97); $p<0.001$], but not in those with a trait-anger score ≥ 19 [HR=1.18 (0.96-1.45); $p=0.11$] (Table 9).

Table 9: Depressive Symptomatology by Anger Predicting Mortality

Category	Covariate	Hazard Ratio	95% Confidence Interval	p-value
Anger <19	Depressive Symptomatology*	2.09	(1.46-2.97)	<0.001
	Age	1.09	(1.04-1.14)	<0.001
	Sex (Females)	1.68	(0.73-3.85)	0.22
	Calories Consumed	1.00	(0.99-1.00)	0.18
	Ever Smoker	1.76	(0.94-3.30)	0.07
	Hypertension	1.54	(0.78-3.07)	0.21
	Non-HDL	1.00	(1.00-1.01)	0.02
	WBC	1.09	(0.95-1.24)	0.19
	WHR [†]	1.82	(1.21-2.74)	<0.01
	HbA1c	1.19	(0.97-1.46)	0.09
Anger ≥ 19	Depressive Symptomatology*	1.18	(0.96-1.45)	0.11
	Age	1.07	(1.03-1.11)	<0.001
	Sex (Females)	1.42	(0.67-0.98)	0.35
	Calories Consumed	1.00	(0.99-1.00)	0.22
	Ever Smoker	1.85	(1.10-3.10)	0.02
	Hypertension	1.99	(1.21-3.28)	<0.01

Table 9 Continued

	Non-HDL	1.00	(0.99-1.00)	0.28
	WBC	1.10	(0.97-1.25)	0.11
	WHR [†]	1.55	(1.07-2.26)	0.02
	HbA1c	1.35	(1.15-1.58)	<0.001

*Residual Value

[†]Accompanying HR (95% CI) per 1 SD change in item score

The same stepwise modeling approach described above was used to investigate Bortner Score and mortality (Table 8). Because an interaction term was not appropriate (none reached a significance level of $p < 0.10$), we used the original Bortner Score as the main predictor and found that it lost significance in multivariable modeling [HR=0.93 (0.77-1.12); $p=0.47$] and that age, sex, non-HDL, fibrinogen, WHR, HbA1c, smoking status, hypertension, WBC, and residual BDI scores remained important predictors of mortality in this model.

3.4 DISCUSSION

Our study has found that depressive symptomatology (residual) is significant in predicting mortality regardless of which covariates were included in the model. In addition, depressive symptomatology (residual) only increased the risk for mortality in those with low trait-anger scores. Type A behavior did not significantly interact with any psychosocial variables, and lost significance in mortality prediction in multivariable modeling.

The importance of depressive symptomatology in those with T1D has been previously demonstrated [170]. The co-existence of depression and T1D is associated with poorer diabetes self-management and metabolic control, decreased quality of life, and higher healthcare usage

[91]. A United Kingdom study found that the prevalence of depression was three-times higher in those with T1D and almost twice as high in those with T2D compared to those free of diabetes [94]. In the EDC study we have previously demonstrated that depressive symptomatology is associated with increased WHR in both genders [97], macrovascular disease and a higher number of complications [171], including incidence of coronary artery disease [96].

Our finding that depressive symptomatology was only detrimental in those who scored low on the trait-anger scale is of particular interest. Trait-anger has been previously demonstrated to be detrimental to health. For example, the Framingham study found that increased trait-anger was associated with total mortality in men in multivariable analyses [110]. However, investigators from the Religious Order Study have reported findings somewhat consistent with ours, although their population greatly differs as the mean age of their sample was 75.4 years and was not diabetes-specific. They found that internally experienced distress (i.e. depressive symptomatology and suppressed anger) was associated with an increased risk of mortality while externally experienced anger, including trait-anger and anger-out, was not [172]. Our data could be similarly interpreted: perhaps participants with higher depressive symptomatology who rated themselves low on the trait-anger scale were not externalizing their distress and were therefore at an increased risk for mortality compared to those participants with higher depressive symptomatology who were externalizing their experiences of distress. In addition, a Japanese study found that while depression was associated with increased risk of cardiovascular disease (CVD) hospitalization or death in those with prevalent CVD, anger was associated with lower risk [173].

As discussed above, the depressive symptomatology and trait-anger interaction we observed may be due to some benefit offered by externalizing distress, in this case in the form of

anger. For example, The Health Professionals Follow-up Study found that moderate levels of anger expression were protective against both stroke and nonfatal myocardial infarction among older males [174]. In addition, the Nova Scotia Health Survey found that decreased constructive anger in men increased the risk of incident CHD [175]. While we did not differentiate between constructive versus deconstructive anger, this may additionally explain our results, as our participants reporting higher trait-anger scores may be constructively dealing with their depressive symptomatology, offering them protection.

We have previously demonstrated an interaction between type A behavior and depressive symptomatology, however this was not found in the current analysis. It appears that this is due to using depressive symptomatology as a residual value (adjusted for anxiety and stress) rather than as an independent variable to assess the interaction. Thus it appears that a portion of depressive symptomatology that interacts with type A behavior is due to anxiety and stress, as well, since the residual values do not interact as the original BDI scores did.

While we saw an interaction between depressive symptomatology and trait-anger in predicting mortality, there were no interactions with hostility, anxiety, stress, or social support. Regarding social support, we only had one scale, the Appraisal Scale, thus perhaps other aspects of social support interact with either type A behavior or depressive symptomatology when predicting mortality in T1D. Interestingly, trait-anger appeared to be important in protecting against mortality in those with high depressive symptomatology, while hostility was not. This may be due to the differences between hostility and anger described above. Future research should focus on studying these psychosocial variables as independent predictors, as they may prove to be independently predictive of mortality, separate from depressive symptomatology and type A behavior.

There were several strengths and limitations regarding our study. Our long-term follow-up allowed us to utilize mortality as an outcome when looking at psychosocial covariates in T1D, which has rarely been examined. In addition, we used numerous psychosocial factors and their interactions to predict mortality, responding to a documented gap in the literature. The limitations of our study include the number of participants excluded due to missing psychosocial data, and the large interval between when our psychosocial factors were measured and mortality; however, we attempted to account for this using Cox proportional hazards modeling. Another limitation was the use of the slightly modified interpersonal support questionnaire; however, we did not find significant associations with this measure (perhaps because the validity had been compromised) in multivariable analyses and thus if interpersonal support did bias our results it was towards the null. Lastly, the lack of follow-up regarding psychosocial data is limiting in that we cannot analyze these variables over time and are confined to baseline data for prediction only.

In conclusion, we demonstrated the importance of assessing the interactions of psychosocial factors when predicting mortality as effects may vary across risk factor categories (e.g. high trait-anger versus low trait-anger). We found that for people with T1D and higher depressive symptomatology, having a high trait-anger score eliminates the increased mortality risk due to this depressive symptomatology. Our findings have potential significant implications for practice; encouraging individuals to externalize their distress may promote emotional well-being and potentially improve diabetes self-management and outcomes. Future research should focus on understanding this depressive symptomatology and trait-anger interaction to potentially improve the lives of those suffering from T1D.

4.0 STRESSFUL LIFE EVENTS PREDICT ELEVATED DEPRESSIVE SYMPTOMATOLOGY, BUT NOT WORSENING OF GLYCEMIC CONTROL

As demonstrated in our previous work as well as in chapter 3.0, depressive symptomatology is an important risk factor for mortality in people with T1D. Described above, previous literature has established a strong association between stressful life events and major depressive episodes in non-T1D populations, but research is lacking in regards to T1D populations. In addition, little is also known about stressful life events and glycemic control in T1D. We thus aimed to investigate the relationship between stressful life events and subsequent depressive symptomatology and change in glycemic control/other diabetes care measures in our T1D population.

4.1 INTRODUCTION

Depression appears to be more prevalent in T1D, with a recent meta-analysis suggesting that people with T1D had nearly four times the prevalence of clinical depression compared to non-diabetic controls [158]. People with T1D and depression are at increased risk of several diabetes-related complications, including coronary artery disease and nephropathy [176]. We previously demonstrated that increased depressive symptomatology over 20 years of follow up increased the risk for mortality in our T1D population [100], and thus investigated potential

factors which may help to contribute to these increased depressive symptomatology. The 2013 ADA Executive Summary for standards of care for people with diabetes stresses the importance of psychosocial aspects of care and notes that screening for problems such as depression, stress, and anxiety are currently poor and insufficient [177]. This emphasizes the need for such screenings in the total care of people with T1D. T1D remains incurable, thus it is important to explore new avenues on which to intervene to improve the elevated mental health burden demonstrated in this population.

Previous literature has established a strong association between stressful life events and major depressive episodes [116]. A study investigating youth with T1D found that stressful life events were associated with greater psychological distress, poorer self-care behavior, and worse control in both cross-sectional and longitudinal analyses [178]. Furthermore, a cohort of African American participants with T1D found that individuals reporting greater incidences of childhood trauma were more likely to experience depressive symptomatology at the time the surveys were completed [120]. Similar findings have been observed in people with T2D [179].

In addition to the potential impact of stressful live events on depressive symptomatology, there is concern for whether stressful life events impact on changes in glycemic control. Poor glycemic control is an important risk factor for the development of diabetes complications and early mortality in those with both T1D and T2D [121]. Key clinical trials have demonstrated the importance of tight regulation of HbA1c in the reduction of these complications [68]. Previous research has also shown that stressful life experiences were associated with continuously poor control or deterioration of glycemic control in those with T1D [122]. The latter study was conducted in a relatively small sample and these findings require replication in a larger study population and in those with diabetes-related complications.

Due to the size of the EDC population it is possible to examine these issues in a larger sample. We thus aimed to investigate the relationship between stressful life events and subsequent depressive symptomatology and change in glycemic control, while assessing other diabetes care measures as potential mediators, in a T1D population.

4.2 METHODS

The EDC study recruited participants diagnosed with T1D between 1950 and 1980 at age <17 years and seen by Children's Hospital of Pittsburgh within one year of diagnosis. Biennial follow-up has occurred since baseline in 1986-1988. Between 1992 and 1994, participants completed a 50-item Life Events Checklist along with other questionnaires and underwent a clinical exam. In order to record significant life events, participants were asked to place a check next to each event that occurred during the previous year (e.g. "Engaged or married," "Birth of a child," "Death of an immediate family member," "Declared bankruptcy or got into debt," etc.). Each question was assigned a weighted score according to the weighting system designed by Holmes and Rahe for their Social Readjustment Rating Scale [180]. Each participant's score for each life event was then added up to a total, composite Life Events score. One question ("convicted of any crime") was omitted because there was no comparable weighted score according to the Social Readjustment Rating Scale. Depressive symptomatology was measured using the BDI, a measure where scores of 16 or higher have been shown to approximate clinically significant symptoms of depression [137], [181]. BDI scores recorded at the same time point as the Life Events Checklist were used in the analysis as these represented the presence of depressive symptomatology after one year's worth of life events.

Fasting blood samples were analyzed for HbA1 (microcolumn cation exchange; Isolab, Akron, OH, USA), and these original HbA1 values were converted to DCCT-aligned HbA1c for all analyses using a regression equation derived from duplicate assays ($\text{DCCT HbA1c} = 0.14 + 0.83[\text{EDC HbA1}]$). HbA1c is reported in the baseline characteristics table as both % and mmol/mol. Change in HbA1c was calculated as the positive change between HbA1c at the time point prior to completion of the Life Events Checklist and the HbA1c measured at the concurrent time point (1992-1994). Because participants were reporting life events over the past year, this measure represented the change in HbA1c that occurred after one year's worth of life events.

The following covariates were chosen based on our previously reported evidence of an association with depressive symptomatology and/or glycemic control and/or diabetes self-care care [83], [122]: age, sex, duration, education, having ever smoked, insulin dose, number of times testing blood glucose levels per week, prevalent major outcomes of diabetes (including coronary artery disease, proliferative retinopathy, amputation, blindness, and nephropathy), body mass index (BMI), and any leisure time activity. Student's t-tests or Wilcoxon rank-sum tests were used to assess the univariate relationship between Life Events score (per 1 standard deviation) and high depressive symptomatology ($\text{BDI} \geq 16$) and to examine the associations between the baseline covariates and depressive symptomatology. Next, to assess the univariate associations between Life Events and these potential covariates, Student's t-tests or Wilcoxon rank-sum tests were again used as appropriate. In addition, correlations were performed between all of the covariates. Those covariates that maintained significance in univariate analyses were then entered into the multivariable logistic regression model as covariates with life events predicting high depressive symptomatology.

Correlations and Wilcoxon rank-sum tests were used as appropriate between baseline covariates and positive change in glycemic control from the past visit to the current visit. Change in HbA1c (as described above) was used as the outcome in a linear regression model with life events predicting change in glycemic control as represented by HbA1c. Assessment of the other diabetes care covariates for potential mediation between stressful life events and positive change in HbA1c was done in the multivariable modeling. All statistics were performed using SAS 9.3 (SAS Institute, Cary, NC).

4.3 RESULTS

Out of 579 living participants, there were 395 participants who were in the Pittsburgh area or able to travel in for the exam and thus completed the Life Events Checklist between 1992-1994; 314 thereof had complete covariate data. Those that were excluded from the analysis were most commonly missing the Life Events Checklist (n=184), Beck Depressive Inventory (n=54), and HbA1c measures (1990-1992) (n=25). These 265 excluded participants differed from the remaining 314 for the following covariates: they were younger, tested their blood sugar more often per week, had higher depressive symptomatology, and were less likely to have an education beyond high school (all $p < 0.05$).

Out of the included 314 participants (mean age=27.9 and diabetes duration=18.8), 31 (9.8%) had a BDI score ≥ 16 . Life event scores ranged from 0 to 443, with a median of 84 points. Participants with high depressive symptomatology (BDI score ≥ 16) had a higher Life Events score, higher prior cycle BDI score, and were more likely to be female, but did not differ for age,

diabetes duration, HbA1c, insulin dose, testing per week, ever smoked, education, or prevalent major outcomes of diabetes (Table 10).

Table 10: Baseline Characteristics for Life Events and High Depressive Symptomatology, 1992-1994 (N=314)

Covariate	Low Depressive Symptomatology (n=283)	High Depressive Symptomatology (n=31)	p-value
Age	34.2 (7.1)	35.9 (7.3)	0.21
Sex; Females %(n)	48.0 (136)	67.7 (21)	0.03
Duration	25.7 (7.3)	27.1 (8.1)	0.32
Insulin Dose	0.69 (0.21)	0.64 (0.19)	0.20
Glucose Testing at Least Once per Week, %(n), Yes	71.3 (202)	74.2 (23)	0.74
HbA1c, %	9.1 (1.4); [76 mmol/mol]	8.9 (1.5); [74 mmol/mol]	0.38
Depressive Symptomatology (1990-1992)	4.0 (1.0-8.0)	14.0 (9.0-18.0)	<0.001
Life Events Score*	78.0 (35.0-139.0)	125.0 (85.0-232.0)	<0.001
Ever Smoked; Yes %(n)	37.4 (106)	45.1 (14)	0.40
Education Above High School; %(n)	71.0 (201)	77.4 (24)	0.45
Prevalent Major Outcomes of Diabetes; Yes %(n)	72.0 (204)	74.1 (23)	0.80

*per 1 SD

We found a significant univariate relationship between Life Event scores and high depressive symptomatology with an odds ratio (OR)=[1.84 (1.34-2.53); $p<0.001$] (Figure 5); (when continuous BDI scores were examined there was a significant association between higher BDI scores and higher life event scores ($p<0.001$)).

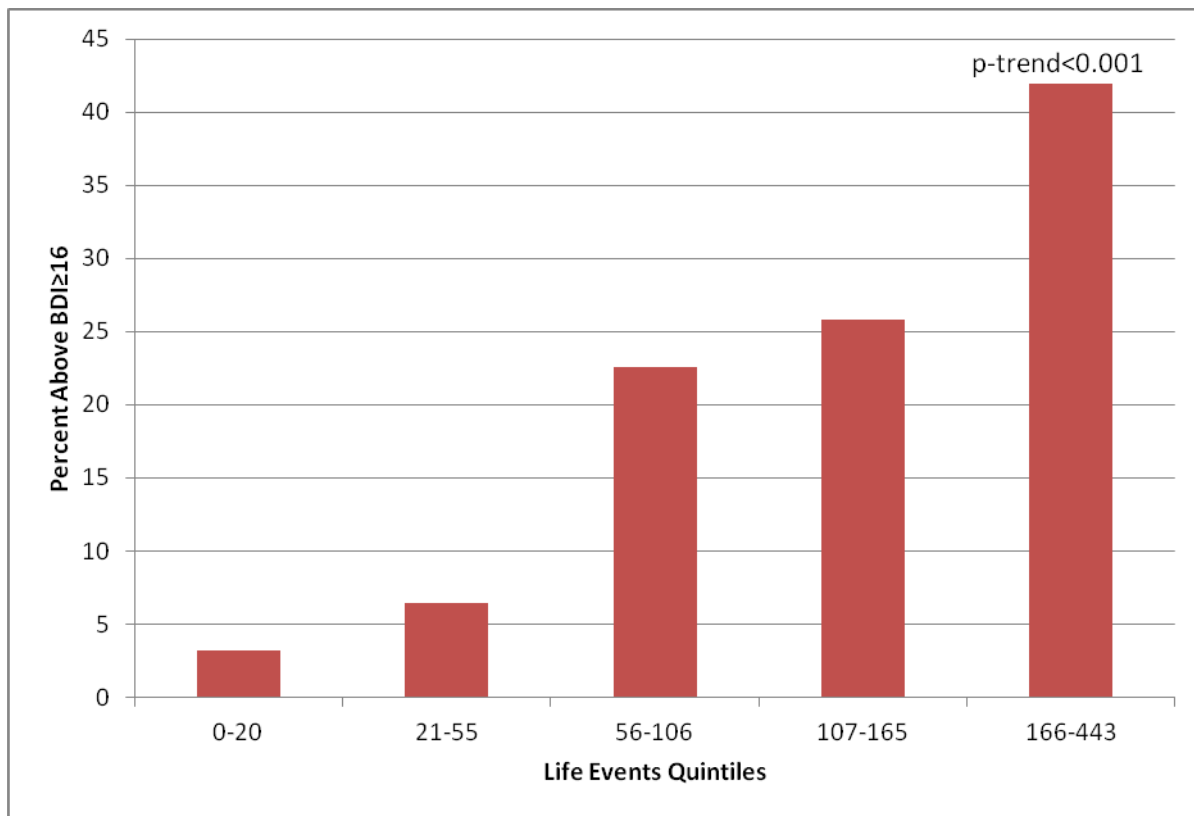


Figure 5: Prevalence (%) of Elevated (≥ 16) BDI Scores by Quintiles of Life Events Scores Over the Prior 12 Months

The relationship was maintained in multivariable modeling adjusting for the covariates described above OR=[1.56 (1.06-2.31); $p=0.02$] (Table 11).

Table 11: Logistic Regression Results: Life Events and High Depressive Symptomatology (N=314)

Variable	Odds Ratio	95% Confidence Interval	p-value
Life Events*	1.56	1.06-2.31	p=0.02
Insulin Dose	1.37	0.16-11.59	p=0.76
Frequency of Testing per Week	0.80	0.43-1.49	p=0.49
Education	0.77	0.28-2.11	p=0.61
Duration	1.01	0.95-1.07	p=0.71
Sex (Females)	0.58	0.23-1.43	p=0.24

Table 11 Continued

Ever Smoked	1.17	0.47-2.91	p=0.72
Prevalent Major Outcomes	1.29	0.45-3.69	p=0.63
HbA1c	0.82	0.58-1.15	p=0.26
Depressive Symptomatology (1990-1992)	1.18	1.10-1.26	p<0.001

*per 1 SD

For the second outcome of interest, change in HbA1c, the mean change between the two time points was $0.17 \pm 1.29\%$ (N=311), i.e. there was an overall increase in HbA1c levels over time. Correlational analyses (Table 12) demonstrated that the increase in HbA1c over time was significantly associated with lower initial levels of HbA1c, BDI score and BMI.

Table 12: Correlations and between Change in HbA1c and Continuous Covariates (N=311)

Increase in HbA1c		
Risk Factors	<i>Correlation</i>	<i>p-value</i>
Life Events Score	-0.03	0.55
Duration	-0.02	0.69
Age	0.04	0.39
HbA1c (1990-1992)	-0.39	<0.001
Insulin Dose	-0.05	0.35
Testing per Week	-0.01	0.76
Depressive Symptomatology	-0.10	0.05
BMI	-0.16	<0.01
Mean Change in HbA1c, %		
Ever Smoked*	<u>Never Smoker:</u> 0.03 (1.05)	<u>Ever Smoker:</u> 0.41 (1.58)
Education	<u>Below High School:</u> 0.20 (1.44)	<u>High School or Above:</u> 0.17 (1.23)
Sex	<u>Male:</u> 0.16 (1.18)	<u>Female:</u> 0.19 (1.39)
Prevalent Major Outcomes	<u>No:</u> 0.30 (1.46)	<u>Yes:</u> 0.13 (1.22)
Any Leisure Time Activity	<u>No:</u> 0.21 (1.34)	<u>Yes:</u> 0.14 (1.25)
Pump	<u>No:</u> 0.19 (1.30)	<u>Yes:</u> -0.33 (1.04)

*p<0.05

Those who had ever smoked had a greater increase in change in HbA1c. After univariate linear regression, there was no relationship between Life Event scores and increased HbA1c ($p=0.67$). After multivariable modeling, there was not much difference in the p-value ($p=0.71$). Previous HbA1c measures, ever smoked status, and prevalent major outcomes of diabetes were the only significant risk factors for an increase in HbA1c. Severity of life events (i.e. life events with weighted scores in the top vs. bottom quintile) was not significantly associated with poorer HbA1c ($p=0.71$).

An investigation of whether diabetes self-care measures (i.e.: frequency of testing, insulin dose, insulin pump, BMI, and leisure time activity) mediated the relationship between stressful life events and change in HbA1c, demonstrated that the relationship between life events and increases in HbA1c did not change ($p=0.70$). Testing at least once per week and BMI were significant covariates for directly predicting positive change in HbA1c ($p<0.05$). The results did not differ when only assessing severe stressful life events.

4.4 DISCUSSION

We demonstrated that higher life events scores predicted clinically meaningful depressive symptomatology (BDI score ≥ 16) up to one year later, even with a small proportion (9.8%) of participants having high BDI scores. We did not, however, find a relationship with change in HbA1c after the occurrence of the life events, nor did we find that any of our other diabetes care covariates notably impacted the relationship.

For our adjusted model, an OR=1.56 can be interpreted such that 1 standard deviation increase in life event score results in a 56% increased odds of having clinically relevant depressive symptomatology. These findings regarding life events and increased odds of depression confirm previous research performed in general populations where investigators found that life events were an independent risk factor for depressive symptomatology or a depressive episode [182], [183]. In regards to the plausibility of this relationship, it has been hypothesized that certain components of clinical disease may be critically affected by the environmental context (e.g. life events) [184]. The results of another previous study [185] as well as our current research suggest that depression is, in fact, responsive to the environment.

We did not, however, find that change in HbA1c resulted from life events. These results differ from much of the previous research in diabetes populations. Investigators studying adolescents with diabetes found that stressful life events were associated with poor glycemic control and also with deteriorating control [186]. This population greatly differed from ours, though, in terms of age. These participants were approximately 10-14 years old at baseline with a mean diabetes duration of 5 years, compared to our population with a mean age of 28 years and diabetes duration close to 19 years at study entry. It has been demonstrated that adolescents with diabetes tend to be in poor control [187], in contrast to adult populations who tend to have better control and may be less likely to have their blood sugar levels affected by stressful life events. We did not find that age or duration were significantly correlated with change in HbA1c in our population, however our participants were mostly middle-aged adults at the time the life events checklist was completed.

Another study in T1D participants free from severe diabetes complications with a mean age of 27 years and 12 years of duration found that those who were in poor or deteriorating

glycemic control were more likely to report severe personal stressors compared to remaining in fair or improving their glycemic control [122]. This finding differed from our results, even when we investigated only the most severe life events scores (top quintile). This difference may be, in part, due to the different methods used to measure stressful life-events (in-depth interviews compared to a self-complete checklist) as well as differences in weighting and classification. We also did not find that other diabetes care measures influenced the relationship between life events and positive change in HbA1c (using all life events scores or the most severe scores). This may be due to people with T1D already experiencing high levels of stress due to the nature of the disease, and thus the additional stresses of life events do not change their diabetes care behaviors.

While we did not find that stressful life events predicted change in HbA1c, we did find a significant relationship between stressful life events and high depressive symptomatology. There were several limitations to our study. First, we had a large number of excluded participants due to a lack of completion of the Life Events Checklist and Beck Depression Inventory; however we did our best to report the differences in populations to assist in interpretation of our findings. Another limitation is that our life events were reported retrospectively, with participants recalling events over the past year. This may have been influenced by the presence of depressive symptomatology at the time of reporting, with those feeling depressed perhaps more likely to report negative events. We attempted to control for this statistically however, by adjusting for the previous time point's depressive symptomatology in multivariable modeling and found that the association was not lost after this adjustment.

In conclusion, we found that increased life events scores predicted increased risk of clinically significant depression, but did not impact any change glycemic control. Future

research should be conducted to assess whether interventions following stressful life events can improve depression outcomes. We hope the findings from our study will continue to improve the mental health, and thus physical health outcomes and mortality risk, in those with T1D.

5.0 INVESTIGATING THE SCORING METHODS AND INDIVIDUAL COMPONENTS OF THE BORTNER TYPE A SCALE IN PREDICTING MORTALITY

Type A behavior has been inversely related to mortality in those with T1D using a modified version of the Bortner Scale. In this current report we explored whether all scoring methods of the Bortner Rating Scale demonstrated a similar association.

5.1 INTRODUCTION

Despite improved survival, people with T1D [8], [11] continue to be at an increased risk of several, often devastating, long-term complications including coronary artery disease and nephropathy [188]. Thus the search for modifiable risk factors, both physiological and psychosocial (such as behavior type), remains important. Studies have shown that people rating themselves as having high type A behaviors tend to focus on achieving and accomplishing more in less time than others and describe themselves as hard-driving [70]. It has been previously shown that in those with T1D, glycemic control differs by behavior type, and this has been reported in both directions, with type A behavior being associated with both poor and good control [75], [130], [131]. This is most likely due to different measures of type A behavior and/or glycemic control and the different types of studies utilized.

We have previously reported a relationship between type A behavior and mortality in those with T1D [83]. Participants with higher type A behavior scores had lower all-cause mortality. However this association was only found in those individuals with low BDI scores [83]. Our finding that type A behavior is protective in T1D is consistent with the literature in the general population which has demonstrated that type A behavior may have different effects on health depending on underlying chronic disease status (for example, it is a benefit in those with prevalent CAD) [71], [189]–[192]. However, whether different Bortner Type A Behavior Scale scoring methods or individual components of type A behavior may serve as better predictors for mortality in T1D is unclear.

By improving our understanding of how type A behavior might protect against mortality it may be possible to develop improved interventions for people with T1D and thus reduce the risk of premature death. In our previously published research [83], we examined a limited number of important and relevant covariates (age, sex, duration, education, physical activity, smoking, BMI, HbA1c, insulin dosage, and depressive symptomatology) along with the Bortner Score to measure type A behavior. We found that type A behavior was predictive of mortality, and that this relationship interacted with depressive symptomatology such that any protection offered was lost in those with higher depressive symptomatology. In this previous analysis we used the original Bortner scale (BO) – the 14 item – to measure type A behavior with reverse coding for five items (#4, 7, 8, 11, and 13(Appendix A)) [132] as recommended by the originators following behavioral interviews. However, there are a number of other scoring methods available. The Bortner Scale can be scored without those five items reversed (BR); as a 7-item scale with the same items reversed (B7R); a 7-item scale with original scoring (B7O); and as separate items (14 individual items (BI)).

In this current report we explore these different scoring methods in order to examine the relationship between type A behavior and mortality in greater detail with the following objectives: 1) to evaluate the different scoring methodologies of the Bortner Type A Behavior Rating Scale, as well as its individual components, in terms of prediction of mortality in our T1D population. 2) to perform multivariable analyses with the strongest predictor from the Bortner scale predicting mortality, 3) to re-evaluate the previously demonstrated interaction of type A behavior and depressive symptomatology in the prediction of mortality using the most predictive Bortner scoring method.

5.2 METHODS

The EDC study recruited participants diagnosed with T1D between 1950 and 1980 at age <17 years and seen by Children's Hospital of Pittsburgh within one year of diagnosis. Biennial follow-up has occurred since baseline in 1986-1988 and data up to the 22-year follow-up are now available. Participants ≥ 18 years of age at study entry completed the Bortner Type A Scale [132] and were instructed to mark on the line where they fell between two different items (more type A versus less type A). Examples of the sentences included "never late" versus "casual about appointments;" "always rushed" versus "never rushed, even under pressure;" and "take things one at a time" versus "try to do many things at once, thinking about what I am going to do next." The five possible Bortner scoring methods were defined as the following: 1) the BO [132]; 2) the BR with items 4, 7, 8, 11, and 13 with scoring reversed [132]; 3) the B7O (Appendix B) [193]; 4) the B7R rescored as above where applicable (i.e. with the relevant items reverse scored); 5) the BI with the original scoring.

Overall mortality was determined as of February 25, 2011 and searches were completed in the Social Security Death Index and the National Death Index. To classify cause(s) of death, death certificates were obtained, plus as appropriate: 1) hospital records; 2) autopsy/coroner's reports; and 3) interview with next of kin regarding the death. The covariates were chosen based on prior evidence for our final mortality prediction model [83], [133]. Depressive symptomatology was measured using the BDI, a measure shown to approximate clinically significant symptoms of depression [137]. The assessment of the other variables is described elsewhere [Chapter 2.0].

In accordance with the specific aims, Cox proportional hazards models were utilized to examine the univariate relationship between baseline Bortner score and overall mortality and to examine the prospective associations between the baseline covariates and mortality. Next, to assess the univariate associations between the different Bortner scoring methods and these potential covariates, Student's t-tests or Wilcoxon rank-sign tests were used as appropriate. In addition, correlations were performed between all of the covariates. Those covariates that maintained significance in univariate analyses were then entered into a final multivariable model as covariates with the Bortner scale predicting mortality. This was repeated for each of the five separate Bortner scoring methods. The final scoring method using the best univariate predictor representing type A behavior was determined and used in mortality prediction. The best univariate predictor was defined as the predictor with the most univariately protective hazard ratio. Lastly, this best scoring method was used to investigate the interaction with depressive symptomatology in predicting mortality. All statistics were performed using SAS 9.3 (SAS Institute, Cary, NC).

5.3 RESULTS

At the EDC baseline exam, of the 592 participants aged 18 years or older, and thus eligible for the BDI and Bortner questionnaires, 97 were excluded due to missing covariate measures: predominantly the Bortner and BDI questionnaires and physical activity measures resulting in 495 eligible participants. Those excluded differed from our included population in the following regards: they were older ($p=0.03$); had a higher WBC count ($p<0.01$); higher WHR ($p=0.03$); were more likely to have ever smoked ($p=0.01$); be male ($p=0.04$); and were less likely to have education beyond high school ($p<0.01$). There were no other significant differences observed, including type A behavior score. Out of these 495 remaining participants, there were 125 deaths (25.2%). These 125 deceased participants differed from the remaining 370 for most of the covariates (Table 13).

Table 13: Baseline Characteristics by Mortality Status (N= 495)

Covariate	Deceased (n=125)	Alive (n=370)	p-value
Age (years)	33.4 (6.3)	27.7 (6.4)	<0.0001
Duration	24.4 (6.5)	18.8 (6.8)	<0.0001
Percent Males (n)	53.6 (67)	47.0 (174)	0.19
Education %(n), Above High School	60.0 (75)	65.9 (244)	0.22
HbA1c (%)	9.1 (1.6)	8.6 (1.4)	<0.01
Insulin Dose	0.73 (0.29)	0.76 (0.21)	0.25
Glucose Testing at Least Once per Week, %(n), Yes	64.0 (80)	63.7 (236)	0.96
WBC	7.4 (2.0)	6.2 (1.7)	<0.0001
Total caloric expenditure in leisure time activity /week	0 (0.0, 525.0)	387.5 (0.0, 1440.0)	<0.0001
WHR [†]	0.86 (0.80, 0.92)	0.82 (0.76, 0.86)	<0.0001
Fibrinogen (mg/dL) [†]	310.0 (270.0, 390.0)	265.0 (210.0, 310.0)	<0.0001
HDL (mg/dL)	49.1 (42.5, 57.9)	53.4 (45.7, 61.8)	<0.01

Table 13 Continued

non-HDL (mg/dL)	163.6 (46.7)	132.4 (38.2)	<0.0001
Daily Calories Consumed	1895.2 (1501.5, 2441.8)	1960.5 (1528.2, 2424.2)	0.47
Ever Smoker % (n), Yes	56.8 (71)	33.7 (125)	<0.0001
Pack years of smoking (n=192)	36.5 (24.8, 48.6)	52.1 (30.4, 91.2)	<0.01
Depressive Symptomatology	8.0 (4.0, 14.0)	5.0 (2.0, 10.0)	<0.0001
Hypertension % (n), Yes	53.6 (67)	25.1 (93)	<0.0001
Lipid Medication % (n), Yes	0.80 (1)	0.54 (2)	0.74

† per 1 SD

Those who died were older, had a longer duration of diabetes, higher HbA1c, higher WBC count, were less physically active, had a greater WHR, higher fibrinogen level, lower HDL, higher non-HDL, were more often smokers, had a higher depressive symptomatology score, were more likely to be hypertensive. Those who died also had lower type A behavior scores for most scoring methods with the exception of individual items #1, 3, 5, 6, 7, 8, 9, and 12 (Table 14).

Table 14: Bortner Scoring Methods by Mortality Status (N=495)†

Covariate	Deceased (n=125)	Alive (n=370)	p-value
BO	169.3 (31.6)	180.0 (29.7)	<0.001
BR	187.2 (26.9)	194.4 (25.1)	<0.01
B7O	88.0 (16.4)	92.0 (15.2)	0.01
B7R	96.3 (18.7)	100.4 (17.7)	0.03
1. Never Late	18.0 (6.5)	17.4 (6.1)	0.36
2. Very Competitive	13.2 (7.0)	14.8 (6.4)	0.01
3. Anticipate what others are going to say	9.0 (6.6)	9.0 (5.9)	0.97
4. Always Rushed	13.0 (5.9)	14.8 (5.4)	<0.01
5. Impatient when waiting	12.2 (7.6)	13.0 (7.1)	0.31
6. Go “all out”	13.7 (6.9)	14.5 (6.2)	0.20

Table 14 Continued

7. Try to do many things at once	10.3 (6.5)	10.1 (5.9)	0.79
8. Emphatic speech	10.8 (6.1)	11.4 (5.4)	0.34
9. Want a good job to be recognized by others	14.6 (6.6)	15.6 (5.8)	0.11
10. Fast eater, walker	12.0 (7.2)	15.4 (6.0)	<0.0001
11. Hard driving	9.2 (5.9)	10.5 (5.7)	0.04
12. Express my feelings	11.8 (7.0)	11.2 (6.6)	0.39
13. Few interests	10.2 (7.0)	8.5 (6.2)	0.01
14. Ambitious	11.9 (6.2)	13.9 (5.5)	<0.01

† per 1 SD

Analyses demonstrated that the individual components, specifically, “fast eater, walker, etc.,” was the most informative in terms of mortality prediction based on its significance (Table 1B), such that lower scores were associated with higher risk of mortality. The “fast eater, walker, etc.” rating was also the most important significant Bortner item after adjustment for age [HR=0.72 (0.60-0.86); $p<0.001$] (Table 15).

Table 15: Univariate Associations between Type A Behavior Scoring Methods and Mortality (N=495)*†

Covariate	Hazard Ratio	Confidence Interval	p-value
BO	0.75	(0.63-0.88)	<0.001
BR	0.85	(0.70-1.02)	0.08
B7O	0.77	(0.65-0.92)	<0.01
B7R	0.91	(0.75-1.09)	0.31
1. Never Late	0.97	(0.81-1.17)	0.80
2. Very Competitive	0.90	(0.75-1.08)	0.29
3. Anticipate what others are going to say	1.00	(0.83-1.20)	0.98
4. Always Rushed	0.73	(0.62-0.87)	<0.001
5. Impatient when waiting	0.94	(0.78-1.12)	0.51
6. Go “all out”	0.88	(0.74-1.04)	0.15
7. Try to do many things at once	1.01	(0.84-1.20)	0.91
8. Emphatic speech	0.93	(0.77-1.11)	0.43

Table 15 Continued

9. Want a good job to be recognized by others	0.79	(0.66-0.95)	0.01
10. Fast eater, walker	0.72	(0.60-0.86)	<0.0001
11. Hard driving	0.80	(0.66-0.97)	0.02
12. Express my feelings	1.03	(0.87-1.23)	0.67
13. Few interests	1.07	(0.90-1.27)	0.41
14. Ambitious	0.83	(0.69-0.99)	0.04

*Adjusted for age

† per 1 SD

Using the “fast eater, walker, etc.” item as the main predictor for mortality, we analyzed the final model comprised of all significant covariates to predict mortality (Table 16).

Table 16: Association between “fast eater, walker, etc.” and all-cause mortality in T1D- Stepwise Cox regression (n=495; 125 events)

	1	2	3	4	5	6	7	8	9	10	11
Fast eater, walker, etc. †	0.62 (0.52-0.74); p<0.0001	0.72 (0.60-0.86); p<0.001	0.71 (0.60-0.85); p<0.001	0.76 (0.60-0.85); p<0.001	0.77 (0.68-0.97); p<0.01	0.81 (0.65-0.97); p=0.02	0.82 (0.68-0.98); p=0.02	0.82 (0.68-0.98); p=0.03	0.80 (0.67-0.96); p=0.01	0.83 (0.70-1.00); p=0.05	0.85 (0.71-1.02); p=0.09
Age		1.09 (1.06-1.12); p<0.0001	1.09 (1.06-1.12); p<0.0001	1.09 (1.06-1.11); p<0.0001	1.08 (1.05-1.11); p<0.0001	1.08 (1.05-1.11); p<0.0001	1.08 (1.05-1.11); p<0.0001	1.08 (1.05-1.11); p<0.0001	1.08 (1.05-1.10); p<0.0001	1.07 (1.05-1.10); p<0.0001	1.08 (1.05-1.11); p<0.0001
Sex			0.70 (0.49-1.00); p=0.05	0.84 (0.59-1.21); p=0.36	1.67 (1.05-1.11); p=0.03	1.48 (0.92-2.38); p=0.10	1.30 (0.81-2.10); p=0.27	1.38 (0.85-2.25); p=0.18	1.53 (0.93-2.50); p=0.08	1.73 (1.04-2.88); p=0.03	1.59 (0.95-2.67); p=0.07
Non-HDL				1.01 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.001	1.00 (1.00-1.01); p<0.01	1.00 (1.00-1.00); p<0.01	1.00 (1.00-1.00); p=0.02	1.00 (0.99-1.00); p=0.09
WHR†					1.66 (1.32-2.09); p<0.001	1.60 (1.27-2.01); p<0.001	1.53 (1.21-1.93); p<0.001	1.57 (1.23-2.00); p<0.001	1.54 (1.21-1.96); p<0.001	1.61 (1.25-2.06); p<0.001	1.54 (1.19-1.98); p<0.001
Fibrinogen†						1.34 (1.14-1.57); p<0.001	1.30 (1.11-1.52); p<0.001	1.23 (1.05-1.44); p=0.02	1.20 (1.02-1.42); p=0.01	1.17 (0.99-1.38); p=0.05	1.18 (0.99-1.39); p=0.05
Depressive Symptomatology							1.03 (1.01-1.06); p<0.01	1.03 (1.01-1.06); p<0.01	1.04 (1.02-1.07); p<0.001	1.04 (1.01-1.06); p<0.01	1.04 (1.01-1.06); p<0.01
HbA1c								1.19 (1.05-1.35); p<0.01	1.21 (1.06-1.37); p<0.01	1.25 (1.10-1.42); p<0.001	1.26 (1.11-1.43); p<0.001
Hypertension									1.72 (1.16-2.53); p<0.01	1.91 (1.29-2.82); p<0.01	1.97 (1.33-2.91); p<0.001
Ever Smoker										1.75 (1.20-2.56); p<0.01	1.61 (1.08-2.39); p=0.01

Table 16 Continued

WBC											1.09 (1.00-1.19); p=0.04
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Final Model= allowed for age, sex, duration, education, calories consumed, total sports, smoking, insulin dose, testing per week, hypertension, HDL, non-HDL, lipid medication, WBC, fibrinogen, WHR, HbA1c, and depressive symptomatology; [†] per 1 SD

We found that the relationship between “fast eater, walker, etc.” and mortality was reduced to borderline significance [HR=0.85 (0.71-1.02); p=0.09]. This best model resulted in age, non-HDL, and fibrinogen as the most influential covariates on the relationship between “fast eater, walker, etc.” and mortality. We tested for an interaction between “fast eater, walker, etc.” and depressive symptomatology based on our previously demonstrated interaction between type A behavior and mortality [83] but it was non-significant (p=0.47).

5.4 DISCUSSION

In this current investigation, we have built on our previous research demonstrating a protective effect of type A behavior on mortality in those with T1D by examining the different scoring methods of the Bortner Scale, including the individual type A components. Overall, we found that “fast eater, walker, etc.” was the most significant predictor of mortality out of all the scoring methods. This association became marginal in multivariable analyses due, most prominently, to the additions of age, WHR, non-HDL, and fibrinogen in to the model.

Through analysis of the different scoring methods, we were able to determine if type A behavior is predictive of mortality regardless of the scoring used, and if there are specific aspects of type A behavior that are most important in our T1D population. We determined that there are, in fact, specific aspects of type A behavior that are most predictive of mortality (most significantly “fast eater, walker, etc.”). As stated above, age, WHR, non-HDL, and fibrinogen had the greatest effect on the relationship between “fast eater, walker, etc.” and mortality. In our analyses, increased inflammation and/or non-HDL in combination with age and a large waist to hip ratio may represent subclinical disease and poor health and therefore reduce a participants’

ability to be a “fast eater, walker, etc.,” eliminating this type A behavior component’s protection against mortality. Lastly, our re-evaluation (using “fast eater, walker, etc.”) of our previously demonstrated interaction of type A behavior with depressive symptomatology was not significant, suggesting different interactions for the single item versus total Bortner score in terms of predicting mortality. This finding showed that the total Bortner scale likely combines multiple underlying traits with different characteristics some of which overlap with depressive symptomatology. For example, perhaps those with higher depressive symptomatology are less ambitious or more likely to sit on their feelings, thus leading to an interaction with depressive symptomatology.

There are a few notable limitations to our study. First, using the individual items of the Bortner Type A Behavior scale on their own has not been a previously validated measure of type A behavior. However, “fast eater, walker, etc.” is one of least likely items to be misinterpreted on the questionnaire and thus there is not a substantial concern for bias surrounding its use. How well it represents overall type A behavior on its own in a T1D population, however, is not studied. Next, using this item as the main predictor was not established a priori, although the purpose of this research was to further explore and understand the protective effect of type A behavior on mortality demonstrated in our previous manuscript and thus exploration of the questionnaire was vital to answer our research questions [83]. Future research needs to be conducted to validate this item in T1D and in other populations, as well. Lastly, a limitation of the study was the missing data regarding, primarily, the Bortner and BDI questionnaires, excluding 97 participants from analyses. However, we described the differences in populations and confirmed that those excluded were not significantly different regarding their type A behavior scores.

In conclusion, we successfully evaluated the different scoring methodologies of the Bortner Type A Behavior Scale and determined that its separate components, specifically “fast eater, walker, etc.,” was the best predictor of mortality in our T1D population. This item needs to be validated in other populations; however, the use of a single item to predict mortality from a behavioral standpoint would be very favorable and efficient in the clinical setting. We conclude that there are, in fact, specific components of type A behavior that play an important role in mortality prevention. We hope future research will be able to use these findings to help develop strategies to delay mortality in people with T1D.

6.0 DISCUSSION

A thorough investigation of psychosocial factors and mortality in people with T1D was performed, with a particular focus on type A behavior and depressive symptomatology. In the first investigation we assessed potential mediating/moderating/confounding effects on the relationship between type A behavior and mortality, which expanded on our previous research where we demonstrated a protective effect of type A behavior on mortality when high depressive symptoms were absent. We determined that in men and women combined, type A behavior was univariately protective against mortality, but the relationship was no longer significant after the other risk factors were considered (most prominently, age (antecedent moderator), non-HDL and WBC (mediators), and fibrinogen (moderator)). When these analyses were performed separately by sex, type A behavior was univariately protective against mortality in men but not in women. In men this relationship was lost in the multivariable modeling, most predominately after WHR (mediator) and age (antecedent moderator) were taken in to account in the type A behavior and mortality relationship. Next, we took this research further by investigating individual components of the questionnaire.

In this brief report, looking at our type A behavior and mortality findings in more depth, we investigated the different scoring methods of the Bortner Rating Scale to determine which was best for predicting mortality in our T1D population. We found that the “fast eater, walker, etc.” item on the scale was the most significant predictor of mortality out of all the scoring

methods. This association was lost in multivariable analyses due, most prominently, to the additions of age, non-HDL, and fibrinogen. There are clinical implications regarding the ease of using one item to screen for potential increased mortality risk. Using one item would ensure time efficiency, which is important to clinicians, and may represent overall health status and/or wellness. This may be important in detecting subclinical disease or a decline in functioning.

Because psychosocial factors are usually investigated as their own, separate constructs, it is important to examine them with other psychosocial factors as well. Thus, the next phase of our study expanded further on this research by investigating which other psychosocial factors interacted with our previously demonstrated relationships between type A behavior and depressive symptomatology and mortality. First, we determined that depressive symptomatology was significant in predicting mortality regardless of which covariates were included in the model. In addition, we demonstrated a significant interaction between depressive symptomatology and anger, and this interaction term remained significant in multivariable modeling, such that depressive symptomatology only increased the risk for mortality in those with low anger scores. Second, type A behavior did not significantly interact with any other psychosocial variables, and lost significance regarding its relationship with mortality in multivariable modeling.

Since we demonstrated that depressive symptomatology increased the risk of mortality, it was thus important to us to understand factors that contribute to the demonstrated detriments of increased depressive symptomatology. Based on the previous literature, we tested our hypotheses that an increase in stressful life events score would lead to clinically meaningful depression and that stressful life events would also result in a change in HbA1c (an additional risk factor for mortality) over the year the events occurred. After analyses, we found that higher

life events scores predicted clinically meaningful depressive symptomatology up to one year later. This was determined despite a small proportion of participants, less than 10%, having high BDI scores ≥ 16 . We did not, however, find a significant change in HbA1c after the occurrence of the life events.

Our first finding, that type A behavior is protective against mortality, fits in with some portions of the literature and differs from others. In the earlier review by Matthews, et al., type A behavior was directly associated with CHD in the general population, but the findings were consistently inverse in chronic disease populations suggesting a protective effect [70]. T1D is a high-risk population, with those suffering from the disease at a higher risk of many complications, including CHD. The protective effect of type A behavior demonstrated in our population aligns with Matthews et. al's hypothesis [70]. In previous literature, type A behavior has been demonstrated to be protective against a number of complications present in those with T1D [171]. Our results align with this finding regarding a protective effect, as well [72]. This latter study performed by Lloyd et al., although cross-sectional, was one of the first papers to conclude that type A behavior showed a protective effect of any kind. Our research was able to expand on this to assess the longitudinal relationship of type A behavior score, while taking it a step further beyond complications to mortality status. A study more recent than most of the type A behavior and T1D studies found a marginal inverse correlation between neuroticism at diagnosis of T1D and glycemic control 12 months later [194]. The authors conclude that this suggests that higher neuroticism is related to better glycemic control. While neuroticism is only a piece of type A behavior, these authors' conclusions were also in the same direction as our findings.

Our previously published inverse univariate relationship between Bortner scores and all cause mortality remained significant during multivariable modeling. However, the addition of BDI scores to the model attenuated the relationship and a significant interaction was observed, such that any protective effect against mortality was limited among individuals with lower BDI scores, while no effect was seen in those with higher BDI scores. This was the first published paper to prospectively examine the relationship between type A behavior and mortality in T1D. Our current study expanded on this to determine which covariates may be responsible for the type A behavior and mortality relationship. The multivariable relationship between type A behavior and mortality was lost in our current report when a greater range of factors were studied. Twenty individuals were not included in both papers hence are discordant. The different result is likely due, in part, to these 20 discordant participants who had twice the mortality compared to the rest of the population, hence their large effect on the results.

Additionally, our investigation of which scoring methods of the Bortner Rating Scale best predicted mortality in those with T1D also expanded the type A behavior and mortality literature. We found that “fast eater, walker, etc.” was the best overall predictor of mortality. However, this item lost significance in multivariable modeling. Nonetheless, if clinicians could use one item to assess behavior type and therefore potential mortality risk, this would be a fast and effective screening tool and marker of overall health. This item needs to be tested and validated in other populations as a protective factor against mortality. It should also be noted that two other items also showed a strong prediction and should also be evaluated in other populations. In addition, these items should be evaluated as to whether they protect against other negative health outcomes, such as CAD or nephropathy.

Our other primary predictor in this research project, depressive symptomatology, was important to study as it affects a large portion of the population with T1D. One study found that only about 50% of clinical depression cases were found to be receiving health care treatment [195]. Prevalent depression also puts individuals at a higher risk of comorbid physical conditions, as well [85][86][87][88]. The risk associated with depressive symptomatology in T1D, or any chronic disease, is expected. One study found that those with T1D were over three and a half times more likely to have depression, were over two and a half times more likely to have a history of depression, and were two times more likely to be on an antidepressant than individuals free from T1D [93]. Previous research in the EDC Study has demonstrated that duration, hypertension, WHR, physical activity, and depressive symptomatology were all significant independent predictors of CAD in women. However, depressive symptomatology did not increase risk for CAD in men [95]. At a later follow-up point in the study, however, both men and women with increased depressive symptomatology were at an increased risk of CAD [96]. This likely reflects that men generally score lower on the BDI thus may require longer to reach a critical level. Another EDC analysis of combined men and women showed that increased BDI significantly predicted CHD even after controlling for hypertension, WHR, white blood cell count, fibrinogen, smoking status, distal symmetric polyneuropathy, and overt nephropathy. However, this relationship became attenuated after the addition of all possible variables in the mediation analysis [96]. Depressive symptomatology has also been found to be cross-sectionally associated with increased WHR in both genders [97] as well as with macrovascular disease and a higher number of complications in those with T1D [98].

In the EDC Study, it thus appears that depressive symptomatology plays an important role in the incidence and progression of diabetes-associated acute and chronic complications.

Our current findings align with these results. Remarkably, although not included in the manuscript due to its close association with mortality, CAD was not the sole mediator in the depressive symptomatology and mortality relationship and did not diminish the significance level to a large degree. There may be several subclinical responses to depressive symptomatology, and the cardiovascular system may not be the primary route, or the only route, in which depressive symptomatology increases mortality risk. Depressive symptomatology may affect the brain, the heart, and the renal system simultaneously. They may also cause participants to have poor self-care habits, as demonstrated in previous literature [91], thus accelerating their disease. Lastly, perhaps depressive symptomatology increases inflammation throughout, causing damage to several systems.

Regarding depressive symptomatology only being detrimental in those participants with a low anger score, perhaps this is due to some benefit offered by externalizing distress, in this case in the form of anger. We did not differentiate between constructive versus deconstructive anger, and this may additionally explain our results, as our participants reporting higher anger scores may be constructively dealing with their depressive symptomatology, offering them protection. This anger distinction should be examined in future research.

Considering the other existing research on depressive symptomatology and subsequent risk of mortality in T1D, the FinnDiane Study Group concluded that in women only, baseline antidepressant agent purchase (their surrogate marker for depression) was associated with an increased mortality risk over nine years of follow-up [99]. These results differ from our findings, because we did not find a sex interaction and thus demonstrated that depressive symptomatology is a significant risk factor for mortality in both men and women. This difference in findings may be due to the differences in how the predictor was measured. The FinnDiane group captured

those in treatment and with severe enough depression to be on medication. It is known that women are more likely to be diagnosed with depression [99], and perhaps they are more likely to seek treatment and medication, thus explaining the association only being seen in women. There is some evidence for this at cycle 10 in the EDC Study, because more women than men with a BDI score ≥ 16 were taking antidepressants, although this was not statistically significant most likely due to the small sample size.

In the EDC Study, we have self-reported depressive symptomatology data and are thus able to capture those with even minimal to mild depression, which we have demonstrated is still detrimental to health. Screening for depression in T1D is extremely important because it has been demonstrated that depressive symptomatology puts patients at risk for increased complications and mortality. Thus, perhaps treatment of depression may help prevent or delay the development of complications and early mortality, and this is discussed in greater detail below.

We did not find that the other psychosocial variables interacted with type A behavior or depressive symptomatology. Although hostility has been linked to CAD in other populations [110], [196], we did not find it was important in the two relationships on which we focused. Hostility may be important as an independent predictor, and although as we did not study this in depth it did not interact with type A behavior or depressive symptomatology. Therefore, it does not seem that type A behavior's protection differs at different levels of hostility, and the same can be said for depressive symptomatology's detrimental effects. Depressive symptomatology was detrimental in those with both high and low hostility. The existing literature investigating the effects of hostility and its components within T1D is extremely limited. There is still a large

gap in the literature regarding the effects of high hostility in those with T1D and this requires further investigation.

Anger, on the other hand, significantly interacted with depressive symptomatology such that depressive symptoms only increased mortality risk in those with low anger scores. Anger has been shown to be detrimental to health in other populations, but there is a significant gap in the literature in those with T1D. While being an overall angry person in the general population is most likely detrimental, this might be different in those with a chronic disease. It can be very distressing and frustrating having to live with T1D. It is a disease that requires daily maintenance and rigorous care. Based on our findings, it seems it may be helpful for those feeling depressed about their disease to express their anger regarding their diagnosis. The concepts of anger in and anger out have been studied as separate constructs [163]. Anger-in has previously been described as having strong overlaps with depression [197]. Anger-out is expressing anger outwardly in ways that may be constructive or detrimental, including physical assaults and hostile verbal assault. It may be informative to study them in detail in people with T1D.

Additionally, as expected, anxiety is more prevalent in the diabetes population than in the general population [114] because living with a chronic disease often results in feelings of nervousness and stress. Our current study, however, did not find that anxiety interacted with either type A behavior or depressive symptomatology in the prediction of mortality. There is also a large gap in the literature surrounding anxiety in T1D, thus future research should focus on independently understanding how this mental state affects risk of morbidity and mortality.

Social support is another important psychosocial construct and it refers to the network of family and friends surrounding a person in their external environment. We studied the appraisal

component of interpersonal support, but did not find that it significantly interacted with type A behavior or depressive symptomatology. The literature regarding social support in those with T1D is very lacking. One study from the Veterans' Affairs demonstrated that peer support might possibly be beneficial in improving glycemic control; however, future research is definitely needed to make any firm conclusions [161]. Social support may prove to be important to study in T1D, as one of the very few studies in T1D found that participants wished to converse about how others manage their T1D in day-to-day life, the interactions experienced with those who do not have T1D, and the emotions one experiences related to their T1D, and found a peer support group to be useful and therapeutic [127]. In addition, a recent review of the effect of peer support on diabetes-related outcomes found that peer support appears to benefit some people with T2D, but that the evidence thus far is too inconsistent to draw definite conclusions [126].

The lack of findings in our current study may be due to our study only using the appraisal scale, thus future research should focus on understanding all aspects of social support in people with T1D. The appraisal scale is rarely looked at in the literature as its own construct. One study investigating social support, stress, and functional status in patients with osteoarthritis found that the appraisal scale was the least predictive of functional status and was not significantly related [198]. Another study, however, found that increased appraisal support reduced the relationship between age and blood pressure in women [199]. Thus, it is difficult to determine whether our null findings regarding the appraisal scale fit in with current literature in either T1D or T2D. In addition, there are three other constructs of support, which should be explored: belonging support, tangible support, and self-esteem support. These are all functions afforded by social relationships.

Because we have demonstrated how detrimental depressive symptomatology may be in people with T1D, it was important to evaluate risk factors for these increased symptoms. Previous literature had established a strong association between stressful life events and major depressive episodes [116], and our findings fit in with this literature. Specifically, a study investigating youth with T1D found that stressful life events were associated with greater psychological distress, poorer self-care behavior, and worse control in investigators' cross-sectional and also longitudinal analyses. Our findings reiterate these results in adults with T1D. Not only is it distressing to suffer from a chronic disease, but also the addition of life events stress appears to cause an even further increase in depressive symptomatology. As discussed above, screening for depressive symptomatology is important in this population, and in particular, patients with high scores of life events should be given greater focus. Overall, the ADA 2014 guidelines stating that psychosocial counseling be regularly provided to those with T1D should be emphasized in all practices [200]. It is just as important for care as going to the endocrinologist and ophthalmologist. If this population is taught how to effectively cope with not only their disease, but with life events that will inevitably arise sooner or later, perhaps they will be prepared with these coping tools to stay happy and feel in control despite the world around them.

Our lack of findings regarding life events and change in glycemic control differ from the limited information existing in the literature, where researchers found that stressful life experiences were associated with maintained poor control over time or deterioration of control in those with T1D [122]. This difference may be, in part, due to the different methods used to measure stressful life-events (in-depth interviews compared to a self-complete checklist) as well as differences in weighting and classification.

While our work addresses some gaps in the literature and increases the focus on psychosocial health, there are many questions left unanswered. It has been previously demonstrated in the literature that treatment of depression in diabetes is effective for improving depression [201]. However, only one-third of diabetes patients with mental disorders receive care. This is unfortunate, as research has shown that treating depression in those with diabetes not only improves depression, but glucose control, as well [202]. One study examined depression treatment using three arms: the chronic care model (collaborative care), psychotherapy, and pharmacotherapy [203]. They found that the chronic care model approach and psychotherapy/diabetes self-care management were effective at improving glycemic control, but it was difficult to tell if this improvement was because of the diabetes education, the reduction in depression, or both. Investigators also found that pharmacotherapy was successful in reducing depressive symptomatology, but had only small effects on glycemic control. Thus they concluded that a combined therapy was best in treating depression in those with diabetes, as the chronic care model improved glycemic control, depressive symptomatology, and quality of life [203]. It is important to note that the majority of depression treatment research has been performed in T2D, and there is very little research available in T1D.

Depression in diabetes is further complicated by diabetes distress. Diabetes distress is important to consider as it overlaps to a considerable degree, although not totally, with depressive symptomatology. Diabetes distress may result because caring for diabetes involves a large amount of self-management behavior [201]. This may leave individuals feeling overwhelmed, fearful of complications, and guilty about poor management. Diabetes distress, below a psychiatric diagnosis of depression, has been associated with poor outcomes [201]. In addition, it is important to consider that the physical symptoms of depression may be difficult to

tease apart from symptoms of T1D. In order to address this issue, we considered how this might affect our findings, and thus removed the physical symptom questions from the BDI questionnaire. The amended questionnaire remained predictive of mortality in our cohort [HR=1.22 (1.04-1.43); p=0.01] per 1 standard deviation, compared to the BDI with all items included: [HR=1.42 (1.22-1.66); p<0.001].

It is difficult to distinguish whether specific symptoms on the BDI are resulting from depression or diabetes distress. Perhaps people who are feeling sad are sad because they are experiencing depressive symptomatology, or because of distress from their diabetes. In addition, sleep may be affected because of either of the above, as may fatigue. However, regardless of the origin of the symptoms detected via the BDI, treatment of depressive symptomatology reduces diabetes distress, and has the potential to reduce the physical symptoms (e.g. fatigue, loss of appetite, loss of interest in sex) if they result from depressive symptomatology. Research presented at the American Diabetes Association's annual scientific meetings (2014) by Larry Fisher showed that symptoms of depression in people with T2D can be significantly reduced through interventions for "diabetes distress [204]." Thus, from a treatment standpoint, it may not initially be imperative to distinguish where the symptoms are originating, as the initial treatment maybe to address distress. However if depressive symptomatology remains specific antidepressant therapy would be appropriate. Thus, the most important next step might be designing and conducting a clinical trial to treat depressive symptomatology in people with T1D using the chronic care model versus usual care, while gathering in depth psychosocial information both before and after the intervention. The clinical trial (randomized by practice) would screen T1D participants for depressive symptomatology and clinical depression and then refer them for care (chronic care model versus usual care (control group)). The chronic care

model is a multifaceted framework for enhancing health care delivery. This method is focused on treating long-term conditions as opposed to acute care, and aims to improve care at the patient, provider, community, and health system levels [205]. The chronic care model is comprised of 5 elements: the community, the health system, self-management support, delivery system design, decision support and clinical information systems. The trial I am recommending should also treat those with minimal and mild symptoms with the chronic care model versus usual care, as well, to determine if reducing even low depressive symptomatology improves outcomes. The outcomes I recommend to be initially measured are glycemic control and psychosocial factors, specifically diabetes distress, as these associations have been demonstrated in other diabetes populations [206] After an appropriate amount of time passed, I recommend assessing the number of incident complications as well as assessing them separately (nephropathy and CAD in particular, as they were demonstrated to be partial mediators [100]) and investigating mortality if possible.

Previous research investigated whether the use of chronic care model elements was associated with higher-quality care for diabetes. Investigators found that greater physician use of the chronic care model in their clinics was associated with higher behavioral care, but not clinical care in this T2D population [207]. These investigators also looked at physiological outcomes, and found that clinician score for use of a chronic care model (the higher the clinician score, the more they utilized the chronic care model and its elements) was associated with lower HbA1c and lower non-HDL. An additional study investigating the chronic care model in T2D found that after the first 12 months of follow up there were clinical, behavioral, psychosocial, and process improvements in subjects who received a chronic care model-based, multifaceted intervention compared to the usual care group [208]. These investigators used the WHO Quality of Well

Being Index-10 (QWB10), which measures perceived current well-being and provides an overall indicator of mental health over the past 2 weeks (i.e. depression, anxiety, energy, sleep, and positive well-being). After three years of follow-up, investigators found sustained improvements for HbA1c level, blood pressure levels, and self-monitoring for all groups. However, they found that QWB10 scores improved in the chronic care model group only. Authors note that it is difficult to determine why QWB10 scores did not improve in the provider education only group because of the very low sample sizes. Perhaps they were underpowered or there may not have been any actual improvements in QWB10. Thus, quality of life would be an additional important construct to measure in the future trial I am recommending. The authors conclude that other sustained improvements may be due to improvements in diabetes care in general. Again, it is important to note that there is a lack of research regarding the chronic care model in T1D, so my proposed trial would add a great deal to the literature.

Intervention studies have been designed to screen for and treat depression to prevent poor outcomes in other populations. For example, Dr. Bruce Rollman was funded to conduct the Hopeful Heart Trial. He and his team screened hospitalized heart failure patients with the Patient Health Questionnaire-2 (PHQ-2) and then also determined vital status at up to 12-months of follow-up. He found that among hospitalized heart failure patients, a positive PHQ-2 depression screen was associated with an elevated 12-month mortality risk, thus demonstrating the importance for an intervention.

It is important to note, however, that in the ENRICHD trial of myocardial infarction patients, they did not find that depression treatment increased event-free survival [125]. Authors found that the intervention improved depression and feelings of social isolation, but the improvement in the psychosocial intervention group compared with the usual care group was

less than expected. This was most likely due to important improvements in usual care patients [125]. In addition, with secondary analyses, investigators found that the risk of death or recurrent MI was significantly lower in patients taking selective serotonin reuptake inhibitors (SSRIs) compared with patients who were not on these medications [209]. Thus, the literature is conflicting as to whether depression treatment can improve mortality. How this treatment would affect increased mortality risk from depressive symptomatology in T1D is unknown, thus further emphasizing the need for a clinical trial of depression treatment in T1D with long term follow-up.

Intervention studies are being conducted in other high-risk populations, thus it seems timely and relevant to conduct similar research in those with T1D. In addition, psychosocial factors in diabetes are currently receiving a great deal of attention [201], perhaps providing a funding opportunity. Previous research regarding depression interventions in T1D were lacking in terms of additional psychosocial factors (e.g. anxiety, coping skills, social support) [210], [211], thus this study would additionally build on previous literature by assessing these factors in addition to depressive symptomatology. Furthermore, only one study assessed health behaviors such as smoking and physical activity, thus the collection of these and other important covariates would be part of the study design. Lastly, long-term follow-up after the intervention is crucial to assessing complication development and mortality in T1D.

As stated above, I would also aim to collect detailed information on these psychosocial factors: anger, anxiety, coping, social support, behavior type, quality of life, and diabetes distress using valid questionnaires in order to assess whether one or more of these contributes to the effectiveness of a depression intervention via the chronic care model. These items could be investigated as potential mediators/moderators or as outcome variables. I hypothesize that those

experiencing increased social support may assist in reducing depressive symptomatology along with the screening/treatment, although this is based on other literature using the full scale [126] as we did not demonstrate a relationship between appraisal support and our outcome variables. In addition, I hypothesize that treatment of depressive symptomatology via the chronic care model will improve quality of life, depressive symptomatology, and glycemic control based on the literature discussed above. Based on my current research, I also hypothesize that those with higher anger scores will have better outcomes than those with low anger scores due to a therapeutic expression regarding the difficulties of living with a chronic disease. In order to assess this appropriately based on my theory regarding the benefits of expressing anger, I would administer both the State-Trait Anger Scale and the Anger Expression (AX) Scale to try and understand the depressive symptomatology and anger interaction in more depth.

In addition to recommending the above clinical trial, I would also recommend redistributing all of the same questionnaires captured at the EDC Study baseline exam again at the 30-year clinic visit, along with additional psychosocial questionnaires that are currently popular for use. This would allow researchers to assess whether any of the psychosocial constructs stayed constant over time, as well as how well a specific psychosocial factor at baseline predicts the others 30 years later. In addition our study would be able to investigate the comparability of older questionnaires to the newer questionnaires (all completed at the 30 year visit). For example, investigators could assess whether the Bortner Rating Scale, which is no longer commonly used, gives similar personality findings as the Eysenck Personality Questionnaire. Furthermore, they could assess whether the two different scales are associated with outcomes (e.g. glycemic control) the same way. For example, the EDC Study could investigate whether state anger, trait anger, anger in, and anger out have similar relationships and

associations with glycemic control and other diabetes care measures. Administering this packet of psychosocial questionnaires would be an inexpensive addition to the 30 year clinic visit exam, and the only negative aspect would be the additional participant burden created by having them complete supplementary paperwork. Having these data at baseline and again at 30 years of follow-up would be a very unique addition to the psychosocial literature as a whole, as well as the T1D literature, as there is little known about long term repeatability of some of these measures.

In order to tie these current research findings together, there are important concepts to take into consideration (Figure 6).

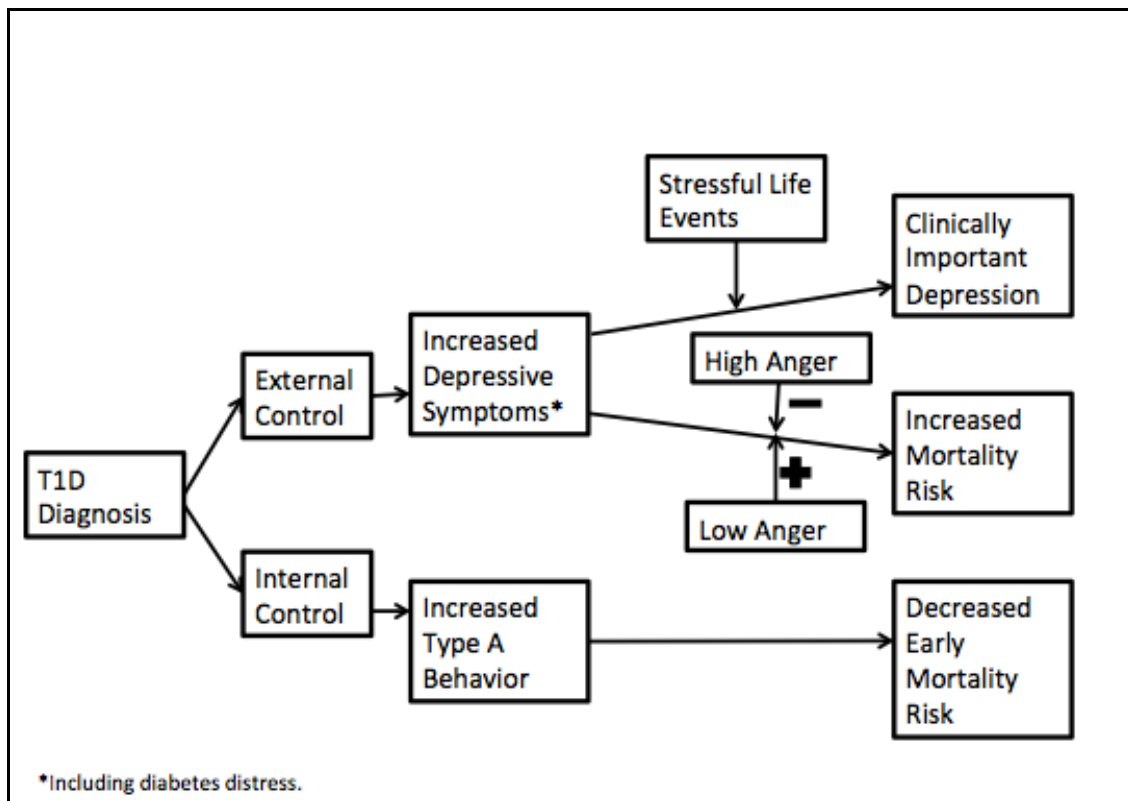


Figure 6: Combining the Locus of Control Theory and Important Psychosocial Risk Factors for Outcome Prediction in T1D.

The locus of control theory refers to the degree to which individuals believe they can control events in their lives [212]. According to this theory, people deal with this control in one of two ways: internally, that is a person believes he/she has control over his/her life, or externally, where a person believes the environment, or fate, has the control and that it cannot be influence [212]. For example, those with internal control believe their hard work will pay off while those with external control believe events are a result of luck or other peoples' influence. Because those with external control believe they have no control over their lives, they tend to become more stressed or depressed compared to internals [213]. On the other hand, those with internal control believe that they can exhibit control over their lives, and if they set things up in such a way that success seems imminent, happiness may be more likely.

A relationship between the health locus of control and diabetes management might exist. Being diagnosed with a chronic disease requiring meticulous care with T1D offering no breaks in care and no days off. Even taking one day off from testing blood glucose or administering insulin can have deadly consequences. It is thus easy to imagine that individuals with an internal locus of control might take responsibility for the care of their T1D, resulting in better glycemic control and health care behaviors, than someone with an external locus who might blame fate or bad luck and become depressed and distressed. It is plausible that someone with type A behavior (described as hard-driving) may also be more likely to have an internal control and believe their actions can influence their health outcomes (e.g. complications), therefore motivating them to adopt the appropriate diabetes care behaviors. This regimented care has the potential to protect them from mortality, as we demonstrated in our results. In addition, being a “fast eater, walker,

etc.” would seem to represent this idea of striving for control, not allowing a chronic disease to slow them down.

The health belief model ties into this, as well, with a particular focus on a few of its components: perceived susceptibility, perceived benefits, perceived barriers, and self-efficacy. Perceived susceptibility maintains that those who believe they are susceptible to a particular health problem will take part in behaviors to reduce their risk [214]. Perceived benefits refer to the belief that taking action will reduce this susceptibility [214]. If those with higher type A behavior are more internal with their control, it is plausible that they believe their actions will reduce their susceptibility to T1D complications thus they are more likely to care for themselves appropriately. Perceived barriers are an individual’s assessment of the obstacles to health care behaviors [215]. These barriers may prevent their undertaking of positive health behaviors. Because those with type A behavior may feel they have control over their diagnosis, they might believe there are fewer barriers to care compared to people with external control. Lastly, self-efficacy refers to how well someone believes they can successfully perform a behavior [215]. People who exhibit internal control, perhaps our people with higher type A behavior, may be more likely to have previously worked to obtain positive outcomes and thus have better self-efficacy due to past successes.

On the other hand, however, it is also easy to see people falling in to the second group already feeling burdened by the idea that they have no control of their lives and on being diagnosed with diabetes having this reinforced. It is understandable that this might result in increased depressive symptomatology [213]. The combination of the toll T1D takes on the body, as well as on the mind through disease burden, and the potential feeling of a lack of control over their situation, may increase the risk of poor health outcomes. If one believes that their poor

health is due to bad luck or insufficient care by their providers, they are most likely not motivated to take action, as their outcomes are out of their control.

It is plausible that this lack of control may cause people to also feel angry. Based on our work, perhaps it is this anger that helps to protect them. For those with external control who believe they were dealt a difficult hand in life, perhaps getting angry about feeling physically and mentally stressed, may offer some protection through anger expression, as described above. Feeling a lack of control over ones' life combined with the physical and mental burdens of the disease does not appear, according to our findings, to produce the best outcomes when internalized. In addition, if people are vocal about their disease distress or depressive symptomatology this may alert those around them to be a support network in their time of difficulty. While we did not find a relationship with social support, again this may be due to us only having the appraisal scale section of the questionnaire. Social support overall may still prove to be important in future research.

In this external control group, they most likely believe that their actions will not reduce their susceptibility to T1D complications. Therefore, regardless of their perceived susceptibility, they do not take action. They also may believe that if they are lucky, in combination with receiving excellent care from their provider, they will see positive results. This success does not require action on their part. The perceived barriers of the health belief model may also prevent them from undertaking positive health behaviors [215]. Because these individuals with external control may be more likely to become stressed or depressed with a T1D diagnosis, these mental health comorbidities may also act as barriers to diabetes care, influencing risk of poor health outcomes. Lastly, people who are externals, and may be more likely to have higher depressive symptomatology, may suffer from low-esteem among other depressive effects, and thus have

lower self-efficacy. This low self-efficacy may result in the belief that one will fail at performing a health care behavior, thus there is no sense in performing it, thereby increasing the risk of poor T1D outcomes.

Furthermore with regard to the locus of control, life events stress would only intensify these feelings of losing control, which in those with external control may increase depressive symptomatology beyond the depressive symptomatology potentially resulting from a T1D diagnosis. With increased life events, the control has extended from internally (i.e. a chronic disease) to the outside environment, as well. It may be that even those with external control who were able avoid stress and depressive symptomatology through living with T1D become stressed or depressed when unanticipated life events occur. Based on our findings, this theory is plausible. People who experienced higher life event scores were at an increased risk of clinically important depressive symptomatology. It should be noted that this was based on their prior depressive symptomatology, as well, so that previous feelings of depression were taken in to account when assessing this relationship. Specifically, if participants reached a median life events score, they were at an almost 50% increased risk of clinically relevant depression. Perhaps our results, which demonstrate the effect of life events on high depressive symptomatology, provide further evidence for the idea that feeling out of control is difficult for some people to tolerate. While this theory seems dismal, we also demonstrated that in our population there were ways people managed to reduce some of their increased risk of mortality brought on by physical and mental burdens. The theorizing of combining type A behavior and depressive symptomatology, based on our results, with the locus of control and health belief models to potentially explain health outcomes in people with T1D is an important avenue of research to pursue in the future.

Through this research project, we have demonstrated that in addition to traditional T1D risk factors, psychosocial factors are also important in outcome prediction. However, there are several limitations to consider. First, we were limited to our psychosocial data assessed only at the baseline visit. Thus, it is difficult to determine causality between the exposures and the outcomes due to the long follow-up between when the exposures and outcomes were assessed. We did our best to account for this using Cox proportional hazards modeling, however this does not definitely determine causality. Next, because of the long follow-up, it is important to consider whether type A behavior changes over time. There are two different outlooks, one is that personality stays constant over the lifetime and the other is that personality changes with age. It is difficult to determine whether our type A behavior measure stays constant over time because we are confined to baseline data only. Thus, the relationship between type A behavior and mortality may change over the course of the study, as people get older. In regards to depressive symptomatology, however, we have it measured over time. I investigated depressive symptomatology as a time-varying predictor in a separate analysis, and found that it predicts mortality not only at baseline, but over 20-years of follow-up, as well. Thus, we are confident that our findings regarding depressive symptomatology and mortality are consistent over the course of the study. Lastly, it is possible that the psychosocial factors impact one another during completion of the questionnaires. For example, perhaps someone with higher depressive symptomatology is more likely to rate themselves as angry. Because we have baseline data only on anger, we cannot assess the temporal relationship between the psychosocial variables. We attempted to study their interactions, however, in Chapter 3.0.

The above recommended screening and treatment regimen may have the potential to have a significant public health impact in not only those with T1D, but with chronic diseases in

general. Implementing mental burden screenings into all clinical settings has the potential to capture many people suffering from depressive symptomatology and diabetes distress. If the appropriate referral networks are put into place, these people can receive treatment to alleviate mental disease and greatly improve their quality of life and potentially even their risk of mortality. There is some evidence that these interventions improve depression, and intervening with the chronic care model may prove to be very important in the eventual treatment of depression in T1D. Because mental diseases like depression are not as tangible as physical diseases does not mean they should not be given secondary attention. Psychosocial factors can be felt just as intensely as physical factors, with depressive symptomatology resulting in a large degree of disease burden. Understanding these feelings and psychosocial cognitions creates a more enriched and complete care model and should be given serious attention in the literature and in the clinical setting.

APPENDIX A: PSYCHOSOCIAL QUESTIONNAIRES: STRENGTHS AND WEAKNESSES

Table 17: Psychosocial Questionnaires: Strengths and Weaknesses

Measure	Questionnaire	Strengths	Weaknesses
Type A Behavior	Bortner Rating Scale	Previously used in T1D populations; high re-test reliability and inter-rater reliability; sufficiently correlated with other type A measures	Self report; scoring discrepancies; no longer used as often as other personality questionnaires.
Depressive symptomatology	Beck Depression Inventory	Validated in both healthy and ill populations; used extensively in the literature; associated with clinically meaningful depression; used in previous T1D research	Self report; does not diagnose clinical depression
Hostility	Cook-Medley Hostility Scale	Predictive of health outcomes; can be broken down into valid subscales that may be more informative than the overall measure in some populations and when examining some outcomes.	Self report; some of the subscales appear to measure other constructs besides hostility; not commonly used in T1D research.

Table 17 Continued

Anger	Spielberger Trait Anger/Anxiety Scale	Only requires a sixth grade reading level; Used across socioeconomic groups; valid for identifying state anger	Self report; does not measure state anger or anger expression.
Anxiety	Spielberger Trait Anger/Anxiety Scale	Only requires a sixth grade reading level; Used across socioeconomic groups; Can be used to diagnose anxiety in combination with the state portion of the scale; Useful in research to differentiate between anxiety and depression.	Self report; does not measure state anxiety.
Interpersonal Support	The Interpersonal Support Evaluation List: Appraisal Scale	Measures the functional components of social support; validated and used since the 1980s.	Self report; only includes one of the interpersonal support scales. One of our questions on the scale was slightly modified.
Stressful Life Events	Life Events Checklist	Comprised of 50 life event items covering a wide variety of events from positive to negative, severe and less severe. The checklist was very similar to the one by Holmes and Rahe and thus we were able to calculate scoring/weighting.	Self-report; differs from the standard, validated life events checklist.

**APPENDIX B: TYPE A BEHAVIOR AND RISK OF ALL CAUSE MORTALITY, CAD,
AND CAD-RELATED MORTALITY IN A TYPE 1 DIABETIC POPULATION: 22
YEARS OF FOLLOW UP IN THE PITTSBURGH EPIDEMIOLOGY OF DIABETES
COMPLICATIONS STUDY**

B.1 INTRODUCTION

The incidence of T1D, which remains incurable, has continued to rise annually by approximately 3% [1]. Unfortunately, prevention is not currently feasible. Therefore, the exploration of T1D complications, untimely mortality and the associated risk factors must continue. Type A behavior has been described as an action-emotion complex, meaning that the behavior is elicited by the outside environment [70]. People characterized as having type A behavior tend to focus toward achieving and accomplishing more in less time than others. Because of these tendencies, these people tend to be competitive, aggressive, time urgent, work-oriented, and can become annoyed if things are not achieved in a time frame they find sufficient [70]. Therefore, it seems that type A behaviors are not a set of personality characteristics that come about due to the environment; rather, the behavior is a result of predispositions within a person that are exhibited due to specific situations [70]. In an earlier review, Matthews et al. noted that although type A behavior was linked to increased CHD risk in the general population, findings were consistently negative in high-risk populations [70]. For example, the prospective

Western Collaborative Group Study (WCGS) found that those with type A behavior experienced an increased rate of CHD compared to type B behavior ($p=0.001$) [153]. However, in their high-risk population who had already undergone a CHD event, type A behavior had a lower CHD-associated mortality rate in those surviving 24 hours or more than those characterized as having type B behavior ($p=0.03$) [154]. Therefore, it appears that type A behavior may have different effects on health depending on underlying chronic disease status.

Little is known about the psychosocial contribution to the increased CAD risk seen in people with T1D beyond depression [96], [171], in particular, whether T1D is an additional high risk group in which the inverse association between type A behavior and CAD/mortality exists. Cross-sectional data from the EDC study have shown (using the Bortner Rating Scale) that participants with multiple complications, including CAD, retinopathy, neuropathy, and/or nephropathy, reported less type A behaviors than those without complications ($p<0.05$) [171]. The long length of follow-up now available in the EDC allowed a prospective analysis of the role of type A behavior in mortality and CAD and we are unaware of other investigations of this relationship. We also investigated the association between type A behavior and CAD-related mortality in those already diagnosed with CAD, and whether the established effect of depressive symptomatology on CAD incidence interacted with or explained any effect of type A behavior.

Thus, the aims of the current study were to investigate the relationships between type A behavior and mortality, type A behavior and incident CAD, and type A behavior and mortality among those with CAD during 22 years of follow-up.

B.2 METHODS

The EDC study is comprised of participants diagnosed with T1D between 1950 and 1980 at age <17 years, seen within one year of diagnosis at Children's Hospital of Pittsburgh. Biennial follow-up has occurred since baseline in 1986-1988, which included questionnaires with physician examinations, and laboratory analyses of urine and blood for the first 10 years and again at 18 years. Data up to the 22-year follow-up are now available. Participants ≥ 18 years of age at study entry completed the Bortner Type A Questionnaire which measures aspects of type A behavior [132] and has been shown to have good test-retest reliability [70]. Participants were asked to circle the dot on the line that represents where they believed they fell between two different sentences. Some examples of the sentences included "never late" versus "casual about appointments," "always rushed" versus "never rushed, even under pressure," and "take things one at a time" versus "try to do many things at once, thinking about what I am going to do next." CAD was defined as myocardial infarction confirmed by hospital records or Q waves on ECG (Minnesota codes 1.1 or 1.2); coronary artery stenosis, defined as $\geq 50\%$ blockage, or revascularization; ischemic ECG, defined using Minnesota Code 1.3, 4.1–4.3, 5.1–5.3, 7.1; angina, diagnosed by an EDC physician; or CAD death (determined by a mortality classification committee).

Overall mortality, including CAD-associated mortality and complication status, was determined as of February 25, 2011. Searches were performed in both the Social Security Death Index and the National Death Index. In order to confirm each death, death certificates were obtained, plus as appropriate: 1) hospital records; 2) autopsy/coroner's reports; and 3) interview with next of kin regarding the death. The underlying causes of death, and the hierarchical order for all contributing causes of death, were determined by a Mortality Classification Committee

consisting of two or more physician epidemiologists. This method is based on standardized procedures [216].

The following covariates were chosen as potential predictors for our final model: age, sex, duration, education, physical activity, smoking, BMI, insulin dosage, HbA1c, and depressive symptomatology. These covariates were chosen because they are previously demonstrated risk factors for CAD and/or early mortality in T1D [133]. Education was assessed using a 5-point scale, i.e.: some high school, high school graduate, some college, bachelor's degree, graduate education beyond bachelor's. Physical activity was assessed using questions about current levels of leisure activities [168], as well as by estimating the energy expenditure over the past week (kcal/week) through use of questions asking about the daily number of flights of stairs climbed, the number of blocks walked daily, and all sports participation that had occurred over the past week. Ever smoked was defined as having had more than 100 cigarettes over their lifetime. Insulin dosage was expressed as the number of units of insulin used per day divided by the participants' weight in kilograms. BMI was calculated as participants' weight in kilograms divided by the square of their height in meters. Fasting blood samples were analyzed for HbA1 (microcolumn cation exchange; Isolab, Akron, OH, USA), and these original HbA1 values were converted to DCCT-aligned HbA1c for all analyses using a regression equation derived from duplicate assays ($\text{DCCT HbA1c} = 0.14 + 0.83[\text{EDC HbA1}]$). Finally, depressive symptomatology was measured using the Beck Depression Inventory (BDI) [217]. The BDI is a 21-item self-report scale that is widely used in both healthy and ill populations. A score of 0–9 indicates minimal depression, 10–18 indicates mild depression, 19–29 indicates moderate depression, and 30–63 indicates severe depression [217]. BDI scores have been shown to approximate clinically significant symptoms of depression [217].

Cox proportional hazards models were utilized to examine the univariate and multivariable relationship between baseline Bortner scores and overall mortality, CAD incidence over 22 years of follow-up, and CAD-related mortality among those with CAD. To assess univariate associations between baseline Bortner score and potential covariates (i.e. age, sex, duration, education, physical activity, smoking, BMI, insulin dosage, HbA1c, and depressive symptomatology), Student's t-test or Wilcoxon rank-sign test was used as appropriate. Cox proportional hazards modeling was used to examine the independent association between Bortner score and each outcome (overall mortality, CAD incidence, and incident CAD death among those with CAD) adjusting for significant baseline covariates. All statistics were performed using SAS 9.3 (SAS Institute, Cary, NC).

B.3 RESULTS

At the EDC baseline exam, 658 participants were seen. One hundred and fifty two participants were excluded from this analysis for having missing covariate measures; however, 60 of these participants were <18 years and therefore not eligible to complete the Bortner or the BDI, and an additional 92 participants were excluded, most commonly, for missing data on the BDI, Bortner, or physical activity measures.

As of February 25, 2011, of EDC participants who completed both the Bortner and the BDI at baseline, and who had complete covariate data (N=506, 250 males and 256 females), there were 128 deaths (25.3%). Those excluded were less likely to have a high school education ($p=0.01$), and were more likely to be smokers ($p<0.01$), but did not differ significantly for age, duration, sex, HbA1c, physical activity, BMI, or depressive symptomatology.

Significant covariate differences existed between those with and without incident CAD for age, duration, physical activity, smoking, BDI, and insulin dosage (Table 18).

Table 18: Baseline Characteristics by CAD Incidence, 1986-1988

	No Incident CAD (n=331)	Incident CAD (n=176)	p-value
Age	26.7 (6.3)	32.1 (6.5)	<0.0001
Sex, %(n), Males	47.1 (156)	54.0 (95)	0.14
Duration	17.9 (6.6)	23.6 (6.9)	<0.0001
Education, %(n), Above High School	65.8 (212)	60.7 (105)	0.25
Total energy expenditure/week (kcal)	1583.0 (646.0, 2961.0)†	1149.0 (448.0, 2238.0)†	<0. 01
Total sports expenditure/week	450.0 (0.0, 1500.0)†	0.0 (0.0, 630.0)†	<0.0001
Smoke Ever, % (n), Yes	32.5 (107)	50.8 (89)	<0.0001
BMI	23.4 (21.6, 25.4)†	23.7 (21.9, 26.1)†	0.25
HbA1c % (mmol/mol)	8.6 (1.5) (70(16.4))	8.7 (1.4) (72(15.3))	0.72
Insulin dosage (Total units/weight)	0.79 (0.24)	0.73 (0.23)	0.01
Bortner Rating Scale	190.1 (25.2)	186.2 (24.6)	0.09
Beck Depression Inventory (BDI)	5.0 (2.0, 10.0)†	6.0 (3.0, 11.0)†	0.01

† Median (Interquartile Range)

A significant trend was demonstrated for both Bortner score (p=0.05) and BDI score (p=0.01) at baseline and CAD incidence (Figure 7).

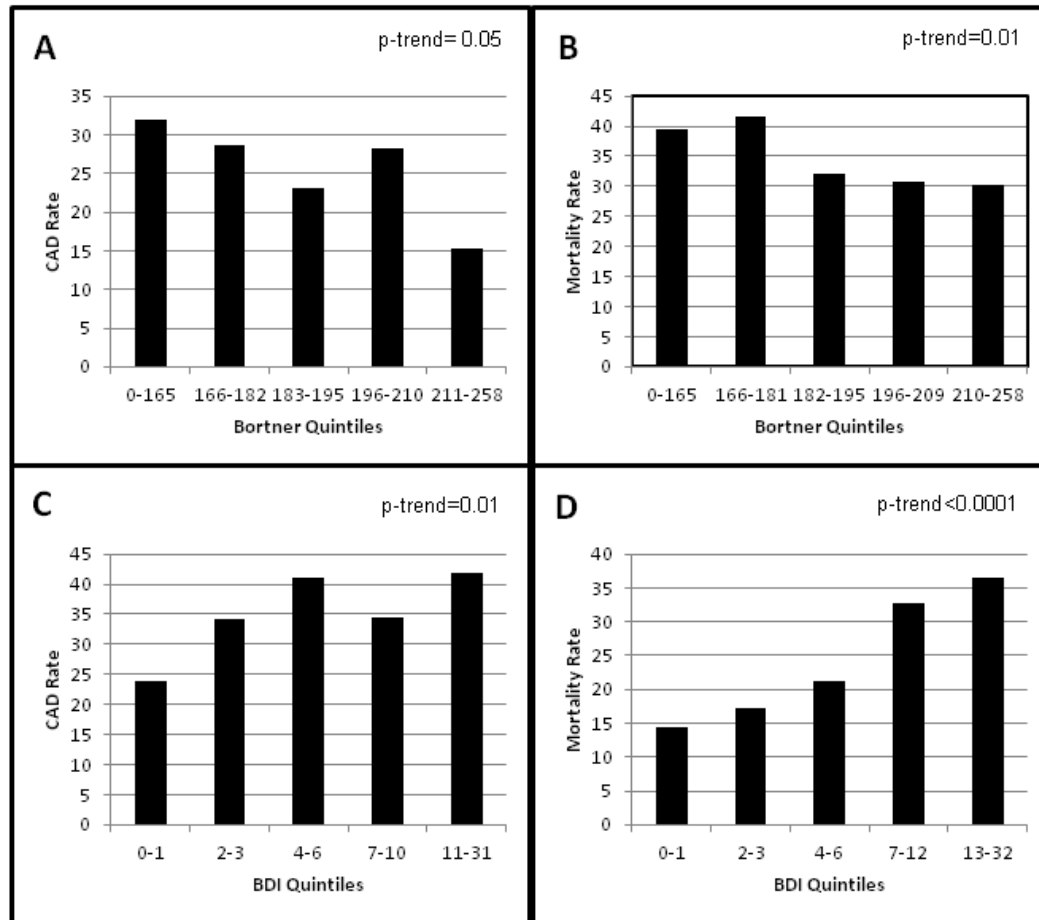


Figure 7: A: Bortner Quintiles and CAD Rate; B: Bortner Quintiles and Mortality Rate; C: BDI Quintiles and CAD Rate; D: BDI Quintiles and Mortality Rate

A borderline univariate relationship was seen between baseline Bortner scores and CAD incidence ($p=0.09$). No significant interaction was observed between Bortner and BDI in relation to CAD incidence.

Differences existed by subsequent mortality for most baseline covariates. Deceased participants tended to be older, with longer diabetes duration, male, less physically active, ever

smokers, had a higher HbA1c and BDI score, and a lower Bortner score compared to survivors (Table 20).

Table 19: Baseline Characteristics (1986-1988) by Subsequent Mortality

	Living (n=378)	Deceased (n=128)	p-value
Age	27.6 (6.5)	33.6 (6.3)	<0.0001
Sex % (n), Males	47.1 (178)	56.2 (72)	0.07
Duration	18.8 (6.8)	24.6 (6.5)	<0.0001
Education, % (n), Above High School	65.6 (248)	60.1 (77)	0.26
Total energy expenditure/week (kcal)	1531.0 (646.0, 2860.0)†	1064.0 (336.0, 2059.0)†	<0.001
Total sports expenditure/week	400.0 (0.0, 1425.0)†	0.0 (0.0, 512.5)†	<0.0001
Smoke Ever, % (n), Yes	33.3 (126)	57.0 (73)	<0.0001
BMI	23.5 (21.9, 25.5)†	23.6 (21.0, 26.3)†	0.91
HbA1c % (mmol/mol)	8.6 (1.4) (70(15.3))	9.0 (1.6) (75(17.5))	<0.01
Insulin dosage (Total units/kg body weight)	0.77 (0.22)	0.73 (0.29)	0.11
Bortner Rating Scale	190.0 (24.2)	182.5 (25.8)	<0.01
Beck Depression Inventory (BDI)	5.0 (2.0, 10.0)†	8.0 (4.0, 14.0)†	<0.0001

† Median (Interquartile Range)

The univariate association between Bortner scores and all-cause mortality is shown in more detail by quintiles ($p=0.01$) (Figure 1B). Those with higher type A behavior tended to be at a reduced risk for mortality with a significant trend ($p=0.01$). Multivariable analyses (Table 20) of the association between type A behavior and all-cause mortality were performed with four models, progressively controlling for covariates.

Table 20: Associate between type A behavior and all-cause mortality in type 1 diabetes- Cox regression**(n=506; 128 events)**

HR (95% CI) for all-cause mortality per 1 unit change in Bortner score					
	Covariate	Hazard Ratio	95% Hazard Ratio Confidence Limits	p-value	AIC
Model 1 ^a	Bortner	0.99	(0.98, 0.99)	0.01	1464.84
	Age	1.10	(1.08, 1.13)	<0.0001	
	Sex	0.65	(0.46, 0.93)	0.01	
Model 2 ^b	Bortner	0.99	(0.98, 0.99)	0.04	1434.22
	Age	1.10	(1.08, 1.13)	<0.0001	
	Sex	0.70	(0.49, 0.99)	0.05	
	Ever smoker	2.05	(1.43, 2.92)	<0.0001	
	HbA1c	1.32	(1.17, 1.48)	<0.0001	
Model 3 ^c	Bortner	0.99	(0.98, 1.00)	0.11	1424.40
	BDI	1.04	(1.02, 1.07)	<0.001	
	Age	1.10	(1.07, 1.13)	<0.0001	
	Sex	0.65	(0.45, 0.93)	0.01	
	Ever Smoker	2.00	(1.40, 2.85)	<0.001	
	HbA1c	1.29	(1.15, 1.45)	<0.0001	
Model 4 ^d	Bortner	0.98	(0.97, 0.99)	<0.01	1421.84
	BDI	0.85	(0.70, 1.03)	0.10	
	Age	1.11	(1.08, 1.13)	<0.0001	
	Sex	0.64	(0.44, 0.92)	0.01	
	Ever Smoker	1.93	(1.35, 2.76)	<0.001	
	HbA1c	1.28	(1.15, 1.43)	<0.0001	
	Bortner*BDI	1.001	(1.000, 1.002)	0.03	

^aModel 1= allowed for age, sex, and duration^bModel 2= allowed for Model 1 + HbA1c, education, smoking, and physical activity^cModel 3= allowed for Model 2 + BDI as a continuous variable^dModel 4= allowed for Model 3 + Bortner and BDI interaction term

Model 1 adjusted for age and sex, with Bortner score remaining significant (p=0.01). Model 2 included age, sex, duration, HbA1c, education, smoking, BMI, and physical activity as covariates and demonstrated that Bortner score continued to significantly predict mortality [HR=0.99; 95% confidence interval (CI): (0.98-1.00); p=0.03]. For every one-point increase on

the Bortner scale, there was a 1% lower mortality risk (Bortner rating scale range: 97-258). However, further adjustment for BDI (model 3), reduced the association between Bortner and mortality ($p=0.11$).

Model 4 tested for an interaction between the Bortner Rating Scale and BDI for mortality (Table 20) as a significant inverse correlation was found between the two ($r=-0.18$, $p<0.001$). This interaction was significant ($p=0.03$), meaning type A behavior is only operative in those with lower BDI scores. Further BDI stratified analyses were then performed. Based on the quintiles determined in our study population (BDI scores: 0-1, 2-3, 4-6, 7-12, and 13-32) (Figure 7, Panel D), we compared the first three quintiles with the upper two quintiles resulting in two categories, a BDI score ≤ 6 versus a BDI score ≥ 7 . A borderline significant protective effect against mortality was seen with higher type A behavior score in the lower BDI quintiles ($p=0.07$), but not with a BDI score >7 ($p=0.97$).

Performing analyses by sex (mean Bortner score in men: 191.1 vs. women: 185.2; $p<0.01$), a significant univariate relationship between Bortner and mortality [0.98, (0.97, 0.99); $p<0.001$] was seen in men but not in women [0.99, (0.98, 1.00); $p=0.12$]. However, a greater proportion of men than women were type A within our population ($p=0.03$). The significant relationship among men remained after multivariable adjustment [0.99, (0.98, 0.99); $p=0.03$], but was attenuated after further adjusting for BDI [0.99, (0.98, 1.00); $p=0.10$]. A significant interaction between Bortner and BDI ($p=0.03$) was noted though stratification by the same cut points of BDI as above did not yield any significant differences. Stratifying by minimal to mild versus moderate to severe depressive symptoms, however, demonstrated men with minimal to mild BDI [0.98, (0.97, 0.99); $p=0.02$] were protected against mortality compared to those with moderate to severe BDI [1.00, (0.97, 1.04); $p=0.63$] in multivariable analyses.

Out of 506 participants, there were 64 CAD-related deaths (12.6%). We found that Bortner significantly predicted CAD mortality [0.99, (0.98, 1.00); $p=0.04$]. The analyses were subsequently repeated excluding non-CAD deaths from the control group (essentially comparing survivors to CAD death (14.3%)), and a significant relationship between Bortner and CAD death was found, as well [0.98, (0.97, 0.99); $p=0.03$].

We then examined the predictive value of Bortner Rating Scale for CAD mortality in those with prevalent CAD. No univariate association was found with death among those with CAD within 22 years of follow-up ($p=0.35$).

B.4 DISCUSSION

We observed a significant relationship between Bortner scores and all-cause mortality, which was attenuated after adjustment for BDI. We also noted the presence of significant effect modification of the relationship between the Bortner and mortality by BDI score. Thus, a borderline significant inverse association between type A behavior and mortality was only apparent among those in the bottom three BDI quintiles, while this relationship was lost in the top two quintiles. Analyses stratifying by gender suggested that only men were protected against mortality with higher type A behavior score, even after adjustment for BDI. However, stratifying by BDI revealed a protective effect of type A behavior only in those with minimal to mild, but not moderate to severe, depressive symptoms. We found a borderline significant relationship between Bortner scores and incident CAD, which was attenuated after adjustment for duration.

To our knowledge, this is the first study to investigate the relationship between type A behavior and all-cause mortality in a T1D population. Strengths of our study are the long follow-up and the completeness of data obtained for our population. In addition to demonstrating the importance of type A behavior and depressive symptomatology, our results affirm the role traditional, important covariates play on CAD development and early mortality in T1D. Those with the highest type A behavior scores were at the lowest mortality risk, which is consistent with most of the literature demonstrating that high-risk populations are protected with greater type A behavior [70], [153], [171]. However, with the addition of BDI to our model, this relationship was attenuated. After determining that the Bortner scale and BDI were inversely correlated, we tested for an interaction between them to determine if the protective effect we observed from high type A behavior was really due to the low depressive symptomatology score in this group. The interaction term was significant, suggesting that type A behavior may be protective against mortality in the absence of depressive symptomatology (although this was only borderline significant). Any protection from type A behavior appears to be lost once the higher quintiles of depressive symptomatology are reached. This suggests that depressive symptomatology is a stronger predictor of mortality than type A behavior in T1D. Indeed, the death rate was 17.8% in the bottom three quintiles, approximately two times higher than in the top two quintiles, at 34.5%.

The importance of depressive symptomatology in T1D is expected, as it has been frequently demonstrated that those with high depressive symptomatology are at an increased mortality [91] and morbidity risk (including diabetes complications) [92]. Co-morbid depression and T1D is also associated with poorer diabetes self-management and metabolic control, decreased quality of life, and higher healthcare usage [91]. Our previous research showed that

BDI significantly predicted CHD even after controlling for hypertension, waist to hip ratio (WHR), white blood cell count, fibrinogen, smoking status, distal symmetric polyneuropathy, and overt nephropathy. However, this relationship became attenuated after the addition of all possible variables in the mediation analysis [96]. Depressive symptomatology has also been found to increase WHR in both genders [97] and appears to play an important role in the incidence and progression of T1D associated complications, as confirmed in our study.

We hypothesized that Bortner scores would continue to be predictive of mortality, even after controlling for BDI, particularly because individuals with diabetes have to adopt regimented control along with other characteristic type A behaviors, such as having to do many things at once, thinking of what they might need to do next, becoming less casual about things, and feeling ambitious [132]. Type A behaviors may increase the efficiency in which an individual cares for their T1D, therefore preventing complications and early mortality. However, depressive symptoms may out-weigh the significance of type A behavior, as demonstrated in our analysis. Adopting type A behaviors in order to better care for a chronic disease like T1D may also partially explain why type A behavior is protective in high-risk, as opposed to the general, populations. Those with greater type A behavior in the presence of a chronic disease may treat symptoms and suspected complications more seriously and intensively than those characterized as having less type A behavior.

Little research exists on depressive symptomatology and subsequent risk of mortality in T1D. The FinnDiane Study Group concluded that in women, baseline antidepressant agent purchase (their surrogate marker for depression) was associated with an increased mortality risk over nine years of follow-up [2.15 (1.34, 3.45)] [99]. Though this association was only seen in women, our results demonstrate a similar relationship. Those with increased depressive

symptomatology were not only at increased mortality risk, but the protection offered by type A behavior disappeared with increased BDI. Depressive symptoms, therefore, appear to play a very important role in predicting mortality in T1D.

Investigating the association between type A behavior and mortality by sex showed that the protective effects of type A behavior are only significant in men. However, these findings may be partially attributable to a lack of power to detect the relationship in women as fewer women had a high type A score. The relationship among men remained until BDI adjustment. We compared those with minimal to mild versus moderate to severe depressive symptoms, and found only those with high type A behavior and less than moderate depressive symptoms were protected against mortality.

It has been previously noted that because type A behavior questionnaires can be interpreted as geared toward work or competitive behaviors, men may respond differently than women [70]. In other words, men may feel it's more socially acceptable, expected, and fitting of their traditional role to declare themselves as "very competitive," "hard driving," and "ambitious" while women may not feel the pressure to fulfill that stereotype. Therefore, our male participants' responses on the Bortner scale may differ compared to women due to social norms, especially in 1980s when the questionnaire was completed. At that time, if women were homemakers, perhaps they felt they were not facing the daily demands of a career and therefore had less type A responses. This is consistent with our data as we saw a statistically higher mean type A behavior score in men compared to women (191.1 vs. 185.2; $p < 0.01$). A study which also administered the Bortner scale in the 1980s found that participants with no or minimal obstructive CAD had higher type A scores compared to those with obstructive disease. After further analysis by sex, the effect was only significant in men, consistent with our findings [218].

We also examined the relationship between Bortner scores and CAD as it is a major contributor to death. In those free of CAD at baseline, type A behavior predicted CAD during 22-years of follow-up, although this was of borderline statistical significance, and this relationship was attenuated after adjustment for duration. Thus, we did not find that in our population, increased type A behavior was protective against CAD or indeed CAD death among those with CAD. Other factors not measured in our study may play a role and further research is needed to determine which other covariates may offer protection against CAD. Our results were not as hypothesized, however it should be noted that type A behavior was also not detrimental to the development of CAD, which supports previous research in other high-risk groups [70], [153]. Because type A behavior was not related to CAD development, we evaluated whether mortality was predicted by Bortner scores based on whether the primary cause of death was CAD or non-CAD related. We found a significant difference between these two groups, with type A behavior protecting against CAD-related death, and again when comparing CAD-death to survivors only. A previous study by Lloyd, et al. concluded that lower type A behavior scores were associated with an increased macrovascular disease risk [171], however the present study is the first we are aware of to demonstrate that type A behavior in T1D is protective against CAD-death, specifically. In a 10-year follow-up study of middle-aged, employed men, specific personality traits that would be considered type A did not predict CAD-death [219]. The literature examining the relationship between type A personality and CAD-death is limited. Our remarkable finding that type A behavior is specifically protective against CAD-death merits further investigation.

Thus far, study findings examining type A behavior in T1D are conflicting and often focused on surrogate outcomes (such as glycemic control and complications) due to short length

of follow-up time. The results of studies examining type A behavior and glycemic control were mixed, with some suggesting no association [75], [77], [220], others a detrimental association [75], [221], and another a protective association of specific type A behaviors (i.e. neuroticism) [82]. However, the majority of these studies were conducted three decades ago with large amounts of bias, which may explain why mixed results were demonstrated. The majority of the previously published studies were conducted cross-sectionally, using very small sample sizes, and used univariate methods of analysis only. Those that utilized multivariable analyses only controlled for a few relevant covariates. Lloyd et al. found that those T1D participants with multiple complications reported less type A behavior than those without any complications ($p < 0.05$) [171]. In a separate study, it was also determined that in men, lower type A behavior score was predictive of an increased WHR [97]. Because type A behavior was not shown to be detrimental in T1D, and protective against complications as a whole and WHR, our hypothesis was generated that with longer follow-up, higher type A behavior may be protective against mortality. Future research needs to take place to examine this relationship in other high-risk populations.

Based on the literature that high-risk groups are protected by their type A behavior, we investigated the relationship between the Bortner Rating Scale and CAD case-fatality rate. We hypothesized that in this very high-risk group of people with both T1D and CAD, type A behavior would be even more protective, but a relationship was not found. This may be due to several reasons, one being that we may have had an insufficient sample size to find a statistically significant result (28 deaths/125 with CAD). Another reason may be that these participants were too unhealthy to benefit from type A behavior at all, being that they have both T1D and a serious complication. Another explanation may be that the type A behaviors were initiated at

too late a time in life, and that T1D and CAD had already done too much physical damage for any protective effect to take place against mortality. Perhaps behavior type is a trait and not a state, and can therefore be modified. If so, this has great implications for care as we can support behavior change to improve self management, improving the health of those living with diabetes. There were several strengths and limitations of our study. As mentioned previously, our long follow-up time allowed for us to use mortality as our outcome, as opposed to a surrogate endpoint such as complication status. Additionally, this was the first study to investigate the relationship between type A behavior and mortality in T1D, providing data where there currently are none. Limitations of our study include our small sample size for detecting incident CAD death among those with CAD, which may have lead to null results. Another limitation is the possibility of residual confounding; however, we feel we included predictors that are essential for investigating mortality in T1D. Furthermore, there were up to 22 years of follow-up time between measuring type A behavior and mortality and/or the onset of CAD; however, we attempted to control for this in the analysis through use of Cox proportional hazards models.

In conclusion, future research is needed to investigate the interaction between BDI and type A behavior, as the latter was only protective in those with low depressive symptomatology. Further research is also needed to explore the protective relationship between type A behavior and CAD-death. Understanding these relationships are important next steps in exploring the effects of psychosocial factors on mortality in T1D.

APPENDIX C: ADDITIONAL BACKGROUND

C.1 MAJOR OUTCOMES OF DIABETES/NATURAL HISTORY

The majority of this excess CVD risk seen in those with T1D is due to atherosclerosis, which is strongly linked to vascular health [222], [223]. Several factors may also influence vascular health and aging, including age, glycemic control, and autonomic neuropathy (AN). AN predicts both cardiovascular events and mortality in those with T1D [224]. Cardiovascular AN is also associated with subclinical CVD such as increased coronary artery calcium score, subclinical left ventricular dysfunction, and increased pulse pressure in normoalbuminuric T1D participants[225], as well as decreased estimated myocardial perfusion [226]. Along with AN, nephropathy has also been shown to be an important predictor of CAD [227]–[230]. A study by Zgibor et al. aimed to create a CHD risk prediction model for T1D. They found that for males, predictors were higher white blood cell count, micro- or macroalbuminuria, lower HDL, and longer diabetes duration. For females, larger waist/hip ratio, higher non-HDL, higher SBP, use of blood pressure medication, and longer diabetes duration were important predictors [231].

Research has shown that adverse changes in CVD function, arterial compliance, and atherosclerosis exist even in adolescence in those with T1D [232]. Carotid intima-media thickness (cIMT) was studied in adolescents approximately 14 years old and cIMT was found to be related to sex and diabetes duration but not age. cIMT was higher in males than in females,

and pulse pressure and duration in males and low-density lipoprotein (LDL) cholesterol, HbA1c, and duration in females showed a significant association with cIMT. Therefore the T1D itself and other cardiovascular risk factors were determined to be important determinants of cIMT [233].

Another determinant of CVD in T1D is diet. One study reported that dietary saturated fatty acid is not associated with CVD or all-cause mortality, while higher fiber consumption, particularly soluble fiber, may assist in the prevention of CVD and all-cause mortality [234]. This is an important avenue for CVD prevention because diet is highly modifiable. Other modifiable risk factors that may help to minimize CVD risk are rigorous management of glycemic control, lipids, and blood pressure [235].

As stated above, nephropathy is an important predictor of CVD and also mortality. Previous research published in 1983 showed that 83% of participants with T1D who developed persistent proteinuria died throughout follow-up compared with 25% of those without [236]. Uremia was responsible for 66% of deaths, with ischaemic heart disease and stroke accounting for 19% of deaths. Forty-nine percent of participants had died within 7 years of the onset of persistent proteinuria [236]. Another early study of people diagnosed between 1933 and 1952 found that in participants free from proteinuria, the relative risk of mortality was approximately 2.0 compared to a relative risk as high as 100.0 in those with persistent proteinuria. In addition, life expectancy was 50% longer in those diagnosed with proteinuria in 1950 compared to participants diagnosed in 1935. This was mainly due to the decreasing incidence of persistent proteinuria overall. In this European population, uremia was responsible for 66% of deaths in those with proteinuria, with CVD being the cause of death for 23% of participants. Mortality from CVD was approximately tenfold higher in participants with proteinuria compared to those

without [237]. It is important to keep in mind, however, that both of these studies were conducted before the 1980s and therefore nephropathy was diagnosed late, only after the appearance of dipstick-positive proteinuria. At this point, kidney damage was already severe and most likely irreversible [238].

Urine albumin excretion (UAE) began to be measured in the 1980s [239], [240], with the first study post-radioimmunoassay demonstrating cross-sectionally that in participants with a UAE rate >20 $\mu\text{g}/\text{min}$, both systolic and diastolic blood pressures were higher compared with those with lower levels of albuminuria/normal albumin excretion. These participants were also more likely to have proliferative retinopathy; however, glomerular filtration rate (GFR) was similar and all participants demonstrated hyperfiltration. Glycemic control also did not significantly differ across the different UAE categories [241]. The majority of newer studies have demonstrated that the cumulative incidences of both persistent proteinuria and of end stage renal disease (ESRD) in those with a diabetes duration of 25–30 years have declined since the studies conducted in the 1980s [9], [242]–[246]. In slight contrast, the European Dialysis and Transplant Association Registry showed that there has been an increase in renal replacement therapy in those with T1D, however this is most likely due to the increasing prevalence of the disease [247]. This may be also be explained such that instead of preventing proteinuria, its onset is delayed through improved diabetes care [238]. However, the incidence of ESRD appears to be lower than that reported in the 1980s, although the difference between investigating centers is considerable [242], [243], [246] and the time from proteinuria diagnosis to ESRD or mortality has greatly improved [248], [249]. After a T1D duration of 30 years, the cumulative incidences of nephropathy was 25% in the DCCT conventional treatment group, 17% in the EDC cohort, and 9% in the DCCT intensive therapy group [129]. Therefore, it may be

that incidence is not increasing, however life expectancy is and therefore the prevalence of those with diabetes living with ESRD is higher. The delay and prevention of microalbuminuria has also improved over time with the use of intensive glucose management. The regression from microalbuminuria back to normal albumin excretion is much higher than in previous decades and the progression to proteinuria has decreased, as well [250], [251]. There is also evidence that proteinuria may regress to microalbuminuria most likely following improvements in blood pressure control and LDL-c [252], [253]. The EDC study also demonstrated that lipid abnormalities and hypertension accelerate nephropathy [254], and the FinnDiane study group also found that lipid abnormalities predicted renal progression [255]. In addition, the progression to nephropathy may also be due in part to genetics [256]. In diabetic mice, it has been shown that the reduced local production of glomerular vascular endothelial growth factor A (VEGFA) promotes endothelial injury, which in turn prompts the progression of glomerular injury. Therefore, perhaps the upregulation of VEGFA in the kidneys of those with T1D protects the microvasculature from injury. It is reasonable to conclude that a reduction of VEGFA may be detrimental in those with T1D [257].

Evidence is conflicting on whether or not the development of hyperfiltration and microalbuminuria necessarily lead to ESRD in those with T1D. A meta-analysis of 10 small studies demonstrated that the presence of hyperfiltration increased the risk of developing micro- or macroalbuminuria by two-fold [258], while a study involving follow-up at the Joslin Clinic demonstrated no increased risk of progression to microalbuminuria with the presence of hyperfiltration [259]. The FinnDiane study has recently shown that participants with hyperfiltration were not more likely to progress to microalbuminuria than those with normal GFRs [260]. One explanation for this may be that currently, only a small number of patients

have chronic hyperglycemia and all patients in their Finnish population have access to insulin and glucose monitors. Perhaps the clinical situations that previously demonstrated hyperfiltration in those with diabetes are no longer prevalent [260]. Therefore it may be more important to monitor and control HbA1c and lipid levels, rather than hyperfiltration, in order to prevent the progression of kidney disease [260].

Neuropathy, defined as “the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes” [261], is one of the most frequent, major complications of diabetes and is the main cause of foot ulceration, Charcot neuroarthropathy, and lower-extremity amputation (LEA) [262]. In a study by Cusick et al., amputation was determined to be the strongest predictor for mortality out of all complications, and there was also an increased risk of mortality as each individual neuropathy-related complication worsened [263]. In another study, a 23-fold increased risk of LEA was found in those with T1D and T2D compared to the general population, with 49% of all LEAs having occurred in those with diabetes [264], [265]. Three large studies done in Europe found that the prevalence of diabetic polyneuropathy was between 23 to 29% in their populations including both T1D and T2D [266]–[268]. In the Bypass Angioplasty Revascularization Investigation in Type 2 Diabetes (BARI 2D) study of patients with T2D and heart disease, the prevalence of peripheral neuropathy was found to be 51% [269]. Diabetes-related amputation rates appear to differ by region, as demonstrated by a US study performed, adjusting for age, sex, and race [270], and these results were confirmed a decade later in a separate US study [271]. Two English studies of LEA found regional variations, as well, which is an important addition to the literature as their health care coverage is universal unlike the US [265], [272].

Many factors, including disease severity, co-morbidities, social and individual patient factors, access to and quality of primary care, referral delays, and availability of specialist resources, influence the decision of whether or not to amputate as well as the risk of amputation [273]. Another risk factor for amputation in addition to diabetes itself is peripheral artery disease (PAD). In those with PAD, infection was a specific predictor of non-healing, which differed from those without PAD [274]. Another study found that primary healing of a foot ulcer was related to co-morbidity, diabetes duration, extent of peripheral vascular disease (PVD), and the type of ulcer present. In those participants with neuropathic ulcers, deep foot infection, site of ulcer, and co-morbidity were related to risk of amputation. In those with neuroischemic ulcers, co-morbidity, PVD, and type of ulcer present were related to the risk of amputation. This study demonstrated that co-morbidities including the prevalence of multiple diseased organs led to an increased risk of amputation in those with diabetes [275].

The International Consensus on the Diabetic Foot (ICDF) was implemented in order to improve the care of patients with foot ulcers and other complications [276]. A study investigated the rates of LEAs over a five year period of time and found that while non-diabetes related LEA rates increased, major diabetes related LEA rates had fallen. This also demonstrates an improvement in care of foot disease in those with diabetes due to improved care [277]. The ICDF also implemented a group to investigate the effectiveness of revascularization, and found that studies demonstrated improved rates of limb salvage associated with revascularization compared with those without revascularization. However, the number of studies and information provided thus far in the literature is lacking such that they were unable to recommend a best method of revascularization [278]. Another improvement in care has resulted from the creation of the foot risk classification of the International Working Group on the Diabetic Foot [279].

The highest prevalence of neuropathy is in those with poor blood glucose control, measured by HbA1c, offering another area for its potential prevention [280]. Both T1D and T2D neuropathy were investigated in a review and were found to differ in regards to prevention efforts. In T1D, glucose control was successful in preventing neuropathy; however, in T2D, glucose control had a small effect on neuropathy prevention [281]. In 2011, the *Experimental Diabetes Research* journal featured articles related to autonomic neuropathy in hopes of drawing attention to this important and frequently-occurring complication and to encourage its screening by physicians [282].

Painful diabetic neuropathy (PDN) is responsible for substantial morbidity and, through the American Academy of Neurology, evidence-based guidelines have been made available for its management [283]. A large, observational study of patients with diabetes in northwest England were assessed for PDN using both the neuropathy symptom score (NSS) and the neuropathy disability score (NDS) [284]. The study found a prevalence of painful symptoms (NSS ≥ 5) and PDN (NSS ≥ 5 and NDS ≥ 3) was 34% and 21%. In 26% of patients without neuropathy (NDS ≤ 2), painful symptoms occurred, and these symptoms occurred in 60% of patients with severe neuropathy (NDS > 8). The authors adjusted for severity of neuropathy, foot deformities, smoking, alcohol, and insulin use and found that the risk of painful neuropathic symptoms in T2D was double that compared to those with T1D. They also found a 50% increased adjusted risk of painful symptoms in women compared with men [284].

New methods for detecting neuropathy have been developed over the years, one of the most popular being the Michigan Neuropathy Screening Instrument (MNSI) for measuring distal symmetrical peripheral neuropathy (DSP). The DCCT/EDIC confirmed that the MNSI is a non-invasive, valid, and effective measure of DSP in those with T1D. They also noted the benefit of

altering the cut point to define an abnormal test from ≥ 7 abnormal to ≥ 4 abnormal items on the questionnaire portion completed by participants. This appears to improve the effectiveness of the MNSI questionnaire [285]. In contrast, not all recommend the use of the MNSI for diagnosis of diabetic neuropathies [286]. Other methods for detecting neuropathy, specifically DSP, include the Vibratron II, NC-stat(®), and Neurometer(®), and two clinical protocols: the monofilament, and as discussed above, the MSNI. These methods are useful in identifying those with DSP, as well as those at risk for amputation, ulcer, and neuropathic pain. The EDC study-Pittsburgh found that the Vibratron II and MNSI demonstrated the highest sensitivity for DSP and pain related to neuropathy, whereas the monofilament had the highest specificity for both as well as the highest positive predictive value. However, it also had the lowest sensitivity. The MNSI demonstrated the highest negative predictive value and Youden's Index and therefore currently demonstrates the best combination of sensitivity and specificity of DSP in those with T1D [287]. The NC-stat is a point-of-care device and performs standard, noninvasive nerve conduction studies. These studies do not require technical personnel. Nerve conduction velocity has proven to be the best predictor of polyneuropathy in those with diabetes, particularly the sural sensory study component of the test [288].

Retinopathy in those with T1D is a prevalent cause of visual impairment and eventual blindness,[289] with it remaining a leading cause of blindness in many countries [290]. Among those living with diabetes worldwide, over one-third are living with retinopathy [291], with proliferative retinopathy being the most common visually impairing lesion in T1D [292]. In a recent meta-analysis using population-based studies from 35 separate countries, it was found that 77% of those with T1D have some form of retinopathy, while 32% have proliferative retinopathy and 14% have diabetic macular edema [291]. At the 25-year follow-up of the Wisconsin

Epidemiologic Study of Diabetic Retinopathy (WESDR), the T1D cohort demonstrated that 97% of participants had developed retinopathy, 42% developed proliferative retinopathy, 29% developed diabetic macular edema, and 17% developed a more serious case of macular edema [293], [294]. There is some evidence, however, that the prevalence and incidence of severe retinopathy is decreasing in the more recently diagnosed T1D cohorts [295].

Screening has become a very important avenue for prevention and treatment [296]–[299], as retinopathy can progress with few visual symptoms [295]. It is also well known in the literature that regular dilated eye exams are important for not only detecting retinopathy, but in treating it as well [290]. The regularity of these exams should be individualized, with those at higher risk (e.g. with a longer duration of T1D) seen more frequently. This should occur even in those without prevalent retinopathy [300]. Fractal analysis has already been utilized in many branches of medicine to characterize the geometric complexity of blood vessels, and “[t]he geometric complexity of the retinal vasculature can be quantified through calculation of fractal dimension from digital retinal images” [301]. A recent advancement in fractal analysis has been displayed by a study in Australia, showing that retinal fractal dimension (measured using the fractal analysis via a computer-based program) is independently associated with early retinopathy signs in those with T1D and therefore performing fractal analysis on fundus photographs appears to show early microvascular damage of the eyes [301]. A study used focus groups to attempt to better understand the barriers to undergoing these retinopathy screenings, and found that patients not attending screenings differed from those that did in that they had lower levels of education, a more recent diagnosis of diabetes, and they less frequently used insulin. Patients that attended screenings more often reported 'knowledge of detrimental effects of retinopathy on visual acuity', 'sense of duty' and 'fear of impaired vision' as their main

incentives to attend [302]. The main barrier determined was the absence of a recommendation by a health-care provider [302], which is a very modifiable barrier and should be addressed by those working in the clinical setting.

A recent study investigating specific risk factors for development and progression of retinopathy using a risk model found that along with duration of T1D, high HbA1c was a significant independent predictor for reaching a treatment end-point [303]. Therefore, this further demonstrates that the lowering of blood glucose can slow the progression of retinopathy[304] and confirms the results found in the UKPDS and DCCT [305]. The DCCT found that for each percent reduction in HbA1c, there was a reduced risk of retinopathy of 30-40% [306]. Another important risk factor for retinopathy in those with T1D is increased blood pressure [300]. A European study investigating the effect of lisinopril on retinopathy in those with T1D found that treatment with a blood pressure lowering agent decreased retinopathy progression, however this only occurred in those where nephropathy was limited [307].

Inflammatory factors may also play a role in the progression and severity of retinopathy [308]. Multiple studies have demonstrated raised levels of inflammatory proteins in the vitreous and the serum of T1D patients with retinopathy [309]. Treating this inflammation has been explored in clinical trials, with one study using intravitreal administration of corticosteroids and finding a reduced progression of diabetic macular edema and the improvement or at least stabilization of visual acuity. Unfortunately, these positive results are usually accompanied by the steroid-related adverse events [295]. In a very recent study, the DCCT found that increased levels of both AGE-LDL and oxidized LDL in immunocomplexes are associated with increased progression to advanced retinopathy in T1D [310]. Another, although unmodifiable, risk factor

appears to be puberty, specifically the length of the prepubertal duration [311]. However, the literature is inconclusive thus far on the subject and further research is needed.

Not only does retinopathy cause visual impairment and blindness, but it is also a marker of other complications [295], including nephropathy [312]. In the EURODIAB IDDM Complications Study, they found that the prevalence of macroalbuminuria for patients with no retinopathy was 1.6%, non-proliferative retinopathy was 9.0%, and proliferative retinopathy was 34.0% [313]. A separate study found that nephropathy occurred almost 3 times more often for patients with proliferative retinopathy at baseline, compared to those free of the complication [314]. The presence of retinopathy is also a marker for increased risk of systemic vascular complications [315]. A double to triple risk of stroke, CHD, and heart failure are also seen in conjunction with retinopathy [316]–[318]. Although many complications are associated with the presence of retinopathy, it is not as likely that retinopathy is the cause, but rather that it is a sign of existing damage in the microcirculatory system and organs.

Damage in the circulatory system causes an increased risk of another serious complication, as well: CBVD, which has long been established for people with diabetes [319]–[322]. This risk of stroke has been associated with changes in the cerebral vessels of people with diabetes [323]. The Nurses' Health Study found that participants with T1D had a six-fold risk of stroke compared to participants free of diabetes. Specifically, risk of thrombotic stroke was eight times higher and 4.5 times higher for hemorrhagic stroke in those with T1D [324]. The pathophysiology of CBVD in those with diabetes is not fully understood, but all blood vessels appear to be affected by the disease. Possible causal mechanisms may involve “excess glycation, endothelial dysfunction, increased platelet aggregation, impaired fibrinolysis, and insulin resistance” [324]. A study done in the UK also found an increased risk of fatal and non-fatal

stroke for those with T1D, with men having an almost fourfold risk compared to participants free of diabetes, and women having an almost fivefold risk [325]. A Swedish study wished to focus specifically on individuals between 15-49 years of age (a somewhat younger age group) admitted to the hospital due to their T1D. They investigated whether or not this had an impact on premature non-fatal or fatal stroke. They also investigated whether the premature stroke risk was due to being admitted for diabetes complications [326]. Investigators found that those in the 15–49 age group at first hospital admission for T1D had a higher risk of premature stroke than those not admitted to the hospital. Both men and women with nephropathy had the highest SIRs of premature stroke.

A large mortality study in the UK [65] confirmed the findings from the World Health Organization multinational study of vascular disease in diabetes, which demonstrated a raised CBVD mortality in those with T1D (however, the WHO had seen considerable variation between the different countries) [327]. The UK study found that CBVD mortality was raised not only in older T1D patients, but within all age groups in their population [65]. Younger age groups have been a focus of CBVD research in those with T1D, and pediatric case-reports have been studied, as well. Pediatric incidents of stroke largely go undiagnosed, however there is evidence that ketoacidosis in T1D may be a risk factor for pediatric stroke, as well as stroke later in life [328]. More research utilizing population-based study designs is needed to make any firm conclusions.

Many risk factors for CBVD are now known for those with T1D. A meta-analysis of the literature regarding glycemic control and risk of CBVD found that that improved glycemic control resulted in substantial reductions in CBVD risk in those with T1D [329]. This meta-analysis therefore further demonstrates the importance of tight glycemic control in those with T1D in order to assist in preventing macrovascular events. A study performed on a population in

Australia did not find a difference in HbA1c levels, however they had a small number of events and this was likely responsible for the null result. Even with their small sample size, however, they found a strong association between low serum HDL-c and ischaemic stroke in their patients without a CBVD background [330]. A larger study found that there is an important risk profile that exists for those with T1D compared to those without, specifically that those with T1D were more likely to have hypertension and small-vessel disease [331]. Also, those with T1D had increased CAD and PAD compared to those free of T1D. Lastly, the study authors found that the cumulative recurrent ischemic stroke rate after 10 years of follow-up was 40.9% [331].

A recently published study investigating the predictors of stroke, as well as the survival afterwards in those with T1D, found that non-HDLc, diabetes duration, and kidney damage and disease were very strong predictors of stroke overall [13]. For ischemic stroke, duration, non-HDLc, WBC count, pulse, and overt nephropathy were all significant predictors, and for the few participants with haemorrhagic stroke, duration, HbA1c, and DBP were important predictors [13]. Study authors also found that the only significant predictor of fatal stroke was HbA1c, and that the overall median survival time after a participant had undergone an incident stroke was 3.8 years. Along with glycemic control, research has demonstrated that control of lipids, hypertension, and prevention of renal damage are especially important in stroke prevention, as is the monitoring of CVD on both a large-vessel and small-vessel level as those with T1D have a much shorter median survival after stroke compared to the general population [332]. cIMT may be a useful tool for predicting stroke in those with T1D [333], however these data are currently limited and future studies would be especially useful.

In conclusion, those with T1D suffer from a number of temporary and chronic complications. The importance of treating prevalent complications as intensely as possible in

order to prevent other complications from occurring should be emphasized in the clinical setting. Also, many modifiable covariates are precursors to many of the major complications, including HbA1c, blood pressure, lipid levels, and inflammation as discussed above. Tight control of blood glucose levels appears to be beneficial in the majority of situations and HbA1c targets should continue to be encouraged by physicians and met by patients. Also, the presence of renal damage appears to be an important risk factor for several of the T1D related complications and testing of patients' urine should be done frequently by physicians and hospitals. Screening and treatment for the risk factors of these complications, as well as for the complications themselves, will continue to improve the early mortality that is potentially associated with living with T1D.

C.2 PHYSIOLOGICAL RISK FACTORS

Until the DCCT, there was a lack of conclusive evidence from clinical trials that lowering HbA1c would in turn lower the development of chronic T1D complications [334]–[336]. The DCCT randomized participants to either intensive blood glucose therapy or conventional therapy. The intensive therapy group used three or more daily insulin injections or treatment with an insulin pump in order to achieve normal values while the conventional therapy group utilized one or two insulin injections per day [68]. The intensive therapy group aimed to fall within the normal range of HbA1c, which was defined as less than 6.05%. Those in the intensive group had an average HbA1c of approximately 7.0% over the course of the study, while the conventional treatment group had an average HbA1c of approximately 9.0%.

While there were many positives to being intensively treated, there were statistically significant differences in adverse events between the two groups based on the treatment regimen.

There was a higher risk of severe hypoglycemia with intensive therapy, but this group did not experience differences in neuropsychological functioning or quality-of-life. Weight gain was also an issue within the intensive therapy group. At five years, patients receiving intensive therapy had gained a mean of 4.6 kg more than patients receiving conventional therapy [68]. Very importantly, however, the intensive therapy group delayed the onset as well as slowed the progression of retinopathy, nephropathy, and neuropathy between 35-70% compared to the conventionally treated group. Early worsening of retinopathy was seen in the DCCT as well, however they demonstrated that this worsening is temporary and intensive treatment is protective after longer follow-up. The DCCT was not able to offer a specific target HbA1c value, but advised getting patients as close to the normal range as possible while ensuring their safety and protection against frequent hypoglycemic events [68].

Glycemic control is extremely important, and in turn so is the self-monitoring of blood glucose levels. Previous research has demonstrated that self-monitoring of blood glucose is associated with improved glycemic control [337]. An additional important issue in monitoring and controlling HbA1c involves the use of continuous glucose monitoring. Continuous glucose monitoring offers detailed information regarding the direction, magnitude, duration, frequency, and causes of fluctuations in blood glucose levels in those with T1D. An additional asset of the continuous glucose monitor is the frequent readings, which supply trend information. These trends can help identify and therefore prevent periods of hypoglycemia and hyperglycemia [338].

A recent meta-analysis aimed to establish the how effective real time continuous glucose monitoring was compared with self monitoring in those with T1D [339]. The investigators found that the key determinants of HbA1c level included baseline HbA1c, age, self monitoring, and frequency of sensor usage. Importantly, they also determined that there was an overall

reduction in HbA1c of 0.30% among those utilizing continuous glucose monitoring compared to self monitoring [339]. Those with the highest HbA1c at baseline and who used the sensor the most frequently benefitted the most. There was however, no difference in the rates of hypoglycemia between the two monitoring groups. Continuous glucose monitoring was therefore effective in reducing HbA1c compared to self-monitoring. The clinical implications of this analysis are significant, because the cost effectiveness of continuous glucose monitoring is now available for calculation for several patient groups based on their HbA1c, sensor usage, and age [339]. A very recent article highlights the improvements made to the continuous glucose monitor using real-time algorithms, and demonstrated that these algorithms enhance the monitors and show clinical importance for hypoglycemic and hyperglycemic alert generation [340].

HbA1c is a very important risk factor for complications and early mortality in those with T1D. Elevated HbA1c levels, particularly those maintained over time, predict an increase, sometimes drastically, of chronic T1D complications [121]. Key clinical trials have demonstrated the importance of tight regulation of HbA1c in the reduction of these complications, and advances in technology have allowed for close monitoring of daily blood glucose levels.

Another essential physiological risk factor for those with T1D are lipid levels [341]. Abnormal lipid levels have been shown to be very important in predicting CAD, specifically in those with T1D [342], [343]. Those with T1D experience glycemia, and in turn oxidative stress which ages the vessels, and therefore the effects of abnormal lipids become apparent at younger ages in this group. When those with T1D do have higher lipid levels, they appear to be at a greater risk of atherosclerosis and eventual CAD than the general population with the same lipid levels [344]. Also importantly, young T1D patients who have not yet developed complications

are the least likely to be treated for their high cholesterol [345], which may put them at risk of complication development/more rapid complication progression. HbA1c plays an important role in the development of abnormal lipid levels. One study found that among their patients not on dyslipidemia medication, a higher HbA1c was significantly related to worse lipid levels except for HDL-c. The associations between HbA1c and any lipid levels among those on dyslipidemia medication were in the same direction, but became insignificant when the investigators compared these patients with those on no dyslipidemia medication [346].

As discussed above, tight glycemic control is beneficial in preventing T1D complications, however, with tighter glycemic control often comes with weight gain. Whether this weight gain associated with glycemic control in the DCCT is related to an increase in lipid levels was investigated [347]. The study demonstrated that intensive blood glucose therapy resulted in similar control in each of the weight gain quartiles. Improvements resulting from the intensive therapy were counterbalanced by the weight gain, and they found that the first quartile of weight gain did not significantly experience a change in weight during the study and therefore had improvements in triglyceride, total cholesterol, and LDL-c levels compared with their baseline values. Therefore, without weight gain, improved HbA1c control resulted in improved lipid levels. However, those in the fourth quartile (the only quartile in the obese BMI range) experienced a significant worsening of lipid levels compared with their baseline measures [347]. Therefore, it appears that intensive glycemic control is beneficial for lipid levels when participants are not gaining excessive amounts of weight due to the therapy. Once an excessive amount of weight is gained, however, it seems it is important to re-evaluate tight glycemic control as the weight of the person alone can increase their risk for complications, rendering the intensive treatment unbeneficial or even harmful. A similar subject yielded the same results:

when predicting insulin resistance, WHR is of particular importance along with lipid levels, hypertension, glycemic control, and family history of T2D [348]. Thus, these results reiterate the relationship between weight and lipids in predicting health outcomes.

In SEARCH, investigators studied the effects of lipid levels in youth with T1D and compared them to the mean lipid levels among control subjects, youth with T1D with optimal HbA1c ($<7.5\%$), and youth with less than optimal HbA1c ($\geq 7.5\%$) after adjusting for age, sex, race and ethnicity, and BMI [349]. The investigators found that in those with T1D and relatively short disease duration of about 4 years, mean lipid levels and prevalence of specific lipid abnormalities were significantly influenced by HbA1c level. Those with T1D and optimal HbA1c had similar lipid profiles and sometimes even better profiles than the control participants. However, youth with T1D and less than optimal glycemic control had higher lipid levels and a greater prevalence of lipid abnormalities than the controls. Overall, the study demonstrated that youth with T1D have significantly elevated apoB levels and more small, dense LDL particles than the control group, regardless of their HbA1c level [349]. Further evidence has demonstrated that increased lipid levels, specifically total cholesterol and non-HDL cholesterol, may be associated with an increased albumin-to-creatinine ratio (ACR) [350]. Another interesting finding is that parental lipid levels are associated with increased lipid levels in youth with T1D, however whether this is the result of genetics, a shared environment, or most likely, a combination of both has not been teased out [351]. This has significant clinical implications, and perhaps monitoring lipids in T1D youth with parents who have high lipid levels may be important in reducing complications later in life.

Lipid levels play an important role in the development of complications [344] and risk factors [350] in those with T1D not only in adult patients, but in youth, as well. Close

monitoring and control of lipid levels [352] along with HbA1c serves to further prevent the development or worsening of T1D related complications. This is especially important as those with T1D may have the same lipid levels as the general population, yet experience an increase in detrimental effects.

Hypertension has detrimental effects on those with T1D, as well. The EDC study found at their 10-year follow-up that a systolic blood pressure (SBP) of 110 mmHg was predictive of CAD and a diastolic blood pressure (DBP) ≥ 80 mmHg was predictive of total mortality, lower-extremity arterial disease (LEAD), and proliferative retinopathy (PR) [352]. Recent work published from the EDC study demonstrated that participants who subsequently developed hypertension after being free of it at baseline were older and had elevated baseline blood pressure (BP), non-HDL-c, AER, and WBC count compared to those who remained hypertension free. Similar results were also found in the DCCT/EDIC study where they demonstrated that higher HbA1c increased the risk for incident hypertension. Also, older age, male sex, family history of hypertension, greater baseline BMI, weight gain during the course of the study, and increased AER were all independently associated with an elevated risk of hypertension in this population [353].

The prevalence of hypertension is related to the development of numerous complications in those with T1D. Ambulatory blood pressure measurements (ABPM) were found to be significantly related to ACR both cross-sectionally and longitudinally [354]. Specifically, DBP during the day was independently associated with the progression to microalbuminuria. As discussed above in the complications section, microalbuminuria precedes many chronic T1D complications, and monitoring BP may be an important way to screen for those at greatest risk of developing microalbuminuria. A separate cross-sectional study found that in those with T1D,

SBP and DBP during sleep were higher in microalbuminuric than in normoalbuminuric participants or in the control group [355]. This demonstrates that not only is daytime BP important, but a rise or steady state during the night (known as non-dippers) is associated with microalbuminuria, as well. Non-dipping was also shown to be independently associated with proteinuria in the EDC study, involving associations with LDL-c and hypertension [356]. The relationship between BP and nephropathy has been confirmed in a prospective study from the DCCT/EDIC group in which study investigators demonstrated that both SBP and DBP are associated with the development of nephropathy [357]. A clinical trial, published in the New England Journal of Medicine, demonstrated that the antihypertensive used, captopril, in their treatment group significantly reduced the rate of renal function decline in those with T1D and nephropathy. In the antihypertensive group, there was an almost one half reduction in the risk of a doubling of the serum creatinine concentration. This was also seen regarding the combined risk of death, dialysis, or transplantation [358]. The investigators concluded that the decrease in proteinuria can be explained by a favorable effect of the antihypertensive on glomerular hemodynamics and glomerular pathology [358]. Unfortunately, the effects of blood pressure on the development of microalbuminuria have been prospectively demonstrated in youth with T1D, as well [359].

Closely tied in with hypertension is another risk factor, smoking. Cigarette smoking has been shown to be associated with arterial stiffness indexes, specifically in those with hypertension [360]. The EDC study found that along with cardiovascular autonomic neuropathy, low HDL cholesterol and cigarette smoking were predictive of increased arterial stiffness indexes [361]. A review of the literature regarding smoking and diabetes found that smoking predicts the onset and progression of nephropathy in those with T1D [362]. T1D smokers were

also shown to have increased frequency of microalbuminuria and poorer kidney function. They also had worse glycemic control and an increased frequency of retinopathy [362]. Since smoking is a modifiable risk factor, clinicians should be sure to discuss smoking cessation with their T1D patients.

Hypertension and smoking are other important physiological risk factor that put those with T1D at an increased risk for the development of complications and even early mortality. It appears that they play a very important role in the development of CAD, both fatal and non-fatal, as well as a decline in renal function. Both CAD and nephropathy are serious T1D complications that increase the risk of death and can also negatively affect the quality of life. Hypertension and smoking in those with T1D should be screened for regularly and treated in order to reduce its impact on complication development and early death.

Briefly mentioned above, inflammation is another unfortunate consequence of living with T1D, and its presence puts patients at an increased risk of complications and early death. A group of participants with T1D, free from macrovascular disease and other major complications, were compared to age and sex-matched controls in order to investigate whether inflammation was higher due to having T1D itself and not due to having accompanying complications. Investigators found that high-sensitivity C-reactive protein (hsCRP), soluble CD40 ligand (sCD40L), soluble intracellular adhesion molecule (sICAM), soluble E-selectin (sE-selectin), soluble P-selectin (sP-selectin), nitrotyrosine, and interleukin-6 (IL-6) levels (all markers of inflammation, oxidative stress, and monocyte function) were significantly increased in subjects with T1D compared with that of control subjects [146]. None of these inflammatory markers were significantly correlated with glycemic control or BMI. This study provided important

information, because inflammation and oxidative stress appear to be elevated even in those T1D participants free from macrovascular disease.

Not only does inflammation occur as a result of having T1D, but it seems to be present even before onset of disease [363]. The combination of islet cell antibodies and inflammation can predict who becomes a patient with T1D, thus inflammation plays a very important role in the disease. Inflammation also can be triggered and cause further vascular damage through hypoglycemia. In both people with and without T1D, hypoglycemia results in elevated levels of inflammatory markers [364]. Inflammation may therefore be an important mechanism in which hypoglycemia causes damage to the vascular system. Other components of T1D, besides the T1D itself, influence inflammation levels, as well. Because endothelial dysfunction and inflammation are some of the first steps in the process of atherogenesis, which is largely responsible for the development of ischemic heart disease and thrombotic strokes, it is imperative to understand what causes them to occur/ accelerates them. YKL-40, a marker of inflammation and endothelial dysfunction, has been measured in those with T1D versus those without. Investigators found that YKL-40 was higher in those with T1D than in those without [365]. Interestingly, after multivariable analysis YKL-40 levels were significantly associated with level of albuminuria. Investigators demonstrated a significant association between YKL-40 levels and increasing levels of albuminuria to the level of microalbuminuria, however no difference was found between those with microalbuminuria versus those with macroalbuminuria [365]. In a Finnish study, both CRP and IL-6 increased as level of albuminuria increased, as well. In this study however, there was also a difference in the marker levels between the microalbuminuria and macroalbuminuria groups [366]. A separate study also found a significant increase in CRP, nitrotyrosine, vascular cell adhesion molecule, monocyte superoxide anion

release, and interleukin-1 release in participants with both T1D and microvascular disease compared with those with T1D [367]. Based on the results of these studies, low-grade inflammation and endothelial dysfunction appear to be very closely linked, with each affecting one another, and therefore each should be treated as a risk factor for both micro- and macrovascular disease.

The DCCT/EDIC group also wished to investigate the role inflammation plays in the development of complications, and therefore studied C-reactive protein and fibrinogen, soluble vascular cell adhesion molecule-1, intracellular adhesion molecule-1, and E-selectin, and fibrinolytic markers mainly cross-sectionally [150]. They found that fibrinogen was the marker most strongly associated with the progression of both internal and common carotid IMT, and that sE-selectin was the marker most strongly associated with nephropathy. The authors stress the clinical implications of their findings, in that they are predictors of future complications and hopefully therefore interventions can take place. sE-selectin has been demonstrated to be predictive for soft CAD in the EDC study [368], demonstrating its possible relationship with other complications, as well.

Lipoprotein-associated phospholipase A₂ (Lp-PLA₂) has been recently studied regarding inflammation as well, and functions as “an enzyme produced by macrophages in advanced, rupture prone, atherosclerotic plaques. It circulates bound primarily to lipoproteins in the plasma and hydrolyses oxidized LDL generating two proinflammatory mediators, oxidized free fatty acids and lysophosphatidylcholine” [369]. Because of the interaction with LDL particles, it is plausible that Lp-PLA₂ may be directly involved in producing atherosclerotic lesions [370]. The EDC study investigators found that those T1D participants with proteinuria, with the highest Lp-

PLA₂ activity and the highest levels of CRP, were almost three times more likely to develop CAD than those participants with the lowest levels in each group [369].

In conclusion, elevated levels of HbA1c, lipids, BP, and inflammation all detrimentally affect those with T1D both on their own and in conjunction with one another. The literature has demonstrated that all of these physiological risk factors put individuals at a high risk of developing complications, as well as further progressing existing complications. The one positive, however, is that each of these risk factors can serve as a measure of current or future organ damage and are therefore clinically important. Elevated levels of all the risk factors should be treated seriously and monitored closely in order to prevent the further progression of complications, or even their incidence all together.

C.3 DIABETES CARE

T1D care, including glucose monitoring and new methods of drug administration such as the insulin pump, have improved over time [371]. Major advances in the care of T1D include the development of quick-acting and long-acting insulins, as well as improved methods for monitoring blood glucose and improved methods for checking blood glucose levels [372]. Before the discovery of insulin in 1921, T1D patients died within just a few years beyond their diagnosis [372]. Although insulin is not considered a cure, its discovery was the first major breakthrough in diabetes treatment. The DCCT was the first study to exhibit the importance of A1c control. They demonstrated that keeping blood glucose levels as close to normal as can be achieved delays the onset as well as the progression of retinopathy, nephropathy, and neuropathy caused by T1D [373]. Investigators also demonstrated that any sustained lowering of blood

glucose is beneficial even with a history of poor control [373]. Previous research has also demonstrated that self-monitoring of blood glucose is associated with improved glycemic control [337]. In more recent diabetes care news, a study demonstrated that continuous subcutaneous insulin infusion resulted in higher quality of life in children and adolescents with T1D [374]. However, further improvements in the prevention of acute and chronic comorbidities through increased education and involvement of patients as well as providers is needed. The EDC study found that awareness of hypertension and hypercholesterolemia increased as their study progressed, but that there was little improvement in their treatment or control [345]. This was particularly noted in the younger age-groups. Clear guidelines are lacking for treating lipid problems in young adults with T1D, and this is likely partially responsible for the findings. Based on the increased risk of chronic complications resulting from hypertension and hyperlipidemia, the investigators note the magnitude of importance (e.g., only 32.1% of those with hypertension in 1986-1988 were controlled and only 28% in 1996-1998, while the rates were 0% for those with hypercholesterolemia in 1986-1988 and 5.5% in 1996-1988) that should be placed on interventions to treat these conditions in all age groups [345]. It also appears that those T1D patients who are diagnosed and being treated for hypertension and hyperlipidemia are also being treated for a chronic complication, meaning that because of care provided for their complication, screening and treatment for these two disorders was done more frequently than in those complications free. The focus should be on screening for and treating these conditions earlier, before these complications develop.

A variety of barriers to care has been thoroughly discussed, and can be summarized in the following diagram (Figure 8 [375]).

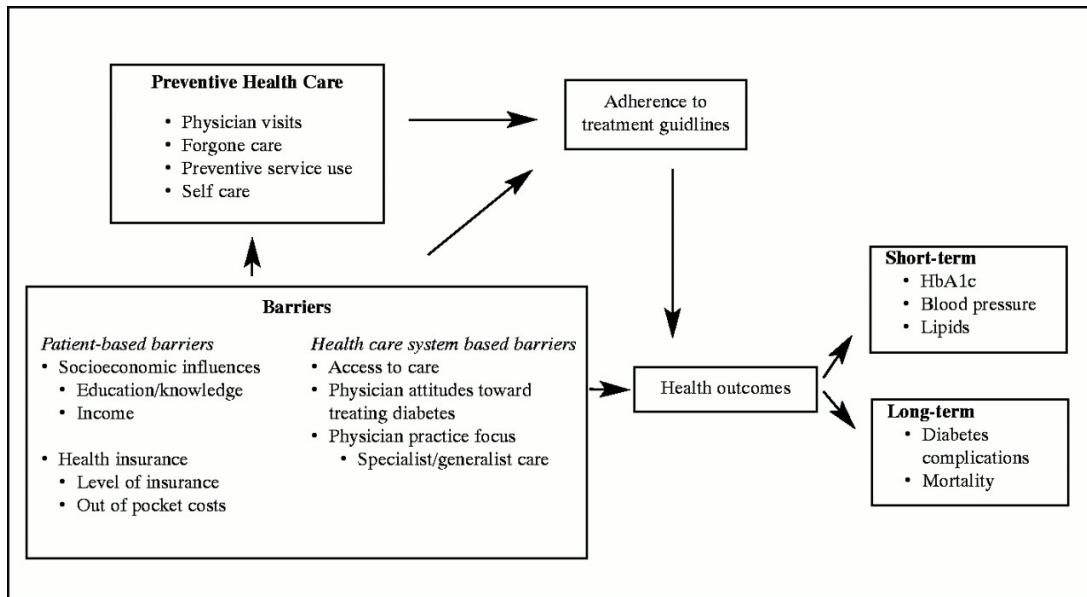


Figure 8: External barriers to care, health care utilization, and outcomes

In this T1D population, there are several aspects of care that play important roles, and combined, can lead to the occurrence of both short-term and long-term complications when prevention and/or adherence to treatment guidelines are lacking.

Caring for a chronic disease such as T1D is not only a physical burden, but is an economic burden as well. The literature has demonstrated that pediatric patients with T1D and good glycemic control have lower costs related to diabetes care spending than those with poor glycemic control [376], [377]. This is due to fewer hospitalizations because of ketoacidosis and other acute T1D complications, therefore decreasing costs. A US study of pediatric patients, with reimbursed costs obtained from January 2004 to December 2005, found that the total diabetes-related costs averaged approximately \$4,730 a person. Ten percent of total costs went towards diabetes education and ambulatory care, while diabetic supplies and medications accounted for a combined 71%. Hospitalizations were 15% of the cost while medication costs were the highest for patients on multiple injections while supply costs were highest for those on an insulin pump [376]. The investigators found that total costs were significantly higher for

those with an HbA1c >8.5%, a more intensive insulin regimen (regardless of distribution method), a single-parent household, female gender, and older age [376].

Because glycemic control has been shown to be an important factor in caring for T1D, it is important to implement interventions to improve control. Nutrition and diet have been demonstrated to be particularly important in caring for T1D. The DCCT study found that participants' adherence to the provided meal plan and their adjustment of food and/or insulin dose due to hyperglycemia, meal size, and content had significantly lower HbA1c levels [378]. Overly treating their hypoglycemia and the consumption of extra snacks not included in the prescribed meal plan had significantly higher HbA1c levels [378]. Along with diet, physical activity has also been shown to be significant in caring for T1D. A meta-analysis demonstrated that aerobic exercise, resistance exercise, mixed exercise (aerobic and resistance training) and exercise of high-intensity significantly decreased blood glucose levels [379]. In order to keep late-onset hypoglycemic episodes from occurring, investigators found that the incorporation of single bouts of sprints into participants' aerobic exercise routine can be recommended. They also demonstrated that regular exercise has a significant effect on acute and chronic glycemic control, specifically aerobic training [379]. There were not enough studies to have adequate power to assess the effects of the other exercises. Both diet and exercise are modifiable methods to improve glycemic control, which in turn reduces complication development and progression.

One area that cannot be overlooked and is becoming increasingly utilized in public health in general is the use of technology. One trial, which investigated this, had one group of adolescents report their blood glucose levels weekly over the Internet to a diabetes care team. The control group received usual care. Unfortunately, their intervention group was non-compliant and they did not have power to detect a significant difference, however they did find

that in those that were compliant, HbA1c was reduced at the end of six months, whereas in the usual care group HbA1c increased [380]. A small pilot study introduced adolescent T1D patients to two different mobile phone applications. One application was in depth and visually stimulating, with pictures to assist in logging physical activity, as well as allowing participants to take pictures of their food for monitoring purposes as well as log their glucose levels. The other group was given the capability of directly contacting diabetes care specialists as well as other adolescents with T1D in order to facilitate communication and support. Although they found no significant decreases in HbA1c in either group from baseline to the end of follow-up (most likely due to a lack of power regarding the 12 participants), they received important feedback regarding the adolescents' preference for the visual application, as well as the increased access to diabetes care professionals. The study investigators are using this information moving forward in designing a clinical trial [381]. Lastly, in regards to the use of technology in attempts to improve care, a review reported that the majority of studies in both T1D and T2D that utilized videoconferencing, mobile phones, telephone calls, and/or feedback letters, showed significant metabolic improvement in 44% of the studies [382]. The use of telemedicine in conjunction with convention care is still a new area of research, but appears to be promising and worth discussing.

A review published in the Lancet investigated the effectiveness of quality improvement (QI) strategies on the management of diabetes (both T1D and T2D) and reported that these strategies were associated with increases in retinopathy, kidney-related, and foot screenings on behalf of the participants over approximately a year of follow-up [383]. In the studies that enrolled patients with low baseline achievement of quality indicators (i.e.: HbA_{1c}, LDL cholesterol, SBP, and DBP), the strategies were associated with larger effects on participants' HbA_{1c}, SBP, DBP, and LDL-c. Each QI strategy's effectiveness was dependent on baseline

HbA1c. Decreases of 0.5% or more in HbA1c were seen for four of the QI strategies, including team changes, case management, patients' education, and promotion of self-management in the trials of patients with 8.0% or greater starting HbA1c. Education of clinicians proved to be important in reducing HbA1c, as well in these particular patients, by about 0.33%. The authors note the importance of future clinical trials studying QI strategies and encourage investigators to describe their interventions in precise detail so that, if successful, they can be effectively repeated and implemented [383]. On a side note, the authors of another literature review concluded that the majority of QI trials contain moderate to high levels of bias [384]. The feedback from the reviews and future well-designed clinical trials will assist in determining which QI strategies and combinations of strategies are the most useful and to encourage implementation in the real world.

Investigators in Italy have also attempted to improve their diabetes care, and developed and validated an educational model, which shifts the emphasis from the traditional one-to-one patient-provider relationship to interactive educational techniques applied in a group setting. They ran a clinical trial to investigate this in participants with either T1D or T2D [385]. The group care participants received group education sessions instead of the usual individual visit, and these took place every 2 to 3 months for those with T1D and 3 to 4 months for those with T2D. One or two healthcare professionals such as doctors, nurses, dieticians, educators, or psychological educators would lead the sessions. The complete program is designed for 2 years of sessions (but continues on after that), each lasting 40-50 minutes, and involves motivational aspects, acceptance of diabetes, psychosocial problems, and coping strategies. At the end of the session, brief individual consultations with the doctor take place to discuss laboratory results, details of the group session, or their yearly diabetes-related check-up [385].

After approximately 6.6 years of follow-up, those with T1D and the group sessions experienced a lower HbA1c (7.4%) compared to the control subjects (8.5%). They evaluated patients' feelings (using propositional analysis) towards either the group care or the usual care, and found those in group care used mostly positive concepts to describe their experiences; however, those in usual care expressed negative concepts. Participants with T1D described the usual visit with the following words or phrases: "What a drag!", "Too much to wait," or "Tension." Those with T2D described the visit as: "Let's hope the results are OK," "Too much to wait," "Anxiety," and "Fear." On the other hand, the group visit T1D patients described the sessions as: "Comparing," "Knowledge," "Educational," and "Friendship." T2D patients in the group setting described their experience as: "Friendship," "I feel good," "I like this," "I learn," and "Interesting" [385]. It appears that this model suggests that collaborative diabetes care should involve a transformation of the relationship between the health care professional and the patient. Those attending the group sessions also experienced an increased sense of personal empowerment in caring for and managing their chronic disease. Perhaps the most important finding of this study was that in those receiving the group care the focus was on health instead of disease, prevention and education as opposed to cure, and successfully made people aware of their choices in relation to their health whereas they may otherwise feel helpless against their disease [385]. The significance of this focus on support in caring for those with diabetes has been discussed in the literature previously [386].

Another European study recruited both professionals and patients and conducted focus groups wishing to identify perceived gaps in current diabetes care, as well as the associated feelings [387]. Investigators found that patients felt they were provided with insufficient diabetes information, and a lack of collaboration between themselves and their provider.

Participants also expressed difficulties in self-management. Both the professionals and patients expressed financial concerns relating to diabetes. The proposed solutions that came up in the focus groups involved reinforcing existing structures, developing educational tools for self-management, and focusing on more coordinated care, communication between the patient and provider, and a feeling of teamwork [387].

One specific area of diabetes care that has been of much focus lately is the transitional period between the pediatric care doctor and the adult endocrinologist. Adolescents experience a gap in their care, in combination with other life changes associated with this age-group, that negatively affect their diabetes care as well as their physical health. A good deal of research is currently focusing on addressing and improving this important problem. In 2011, the American Diabetes Association (ADA) put out recommendations for the transition from pediatric to adult diabetes care [388]. The ADA discusses how these specific patients are at a time in their lives where they are assuming responsibility for their own care and gaining independence from their families. This results in patients under-utilizing available healthcare, having poorer glycemic control, and experiencing an increase in acute and chronic complications. Within research, there is a real lack of well-defined criteria to determine when a patient is ready to transition from their pediatric doctor to an adult doctor. Another large issue is that many patients in emerging adulthood face gaps in their health insurance [388]. The introduction of high-risk behaviors, such as smoking, alcohol, and drug abuse, is also common. In research, there is a complete lack of controlled trials to test validated transition programs, thus the only collected data are through observational studies or uncontrolled data.

Children's Hospital of Boston also addressed the issues involved with transitioning from pediatric to adult care. They mailed emerging adults, between the ages of 22 and 30, a survey to

evaluate the transition process [389]. All participants were being seen by an adult care clinic. The mean age of their responding population was 19.5 years and 34% of these respondents reported a gap >6 months in transitioning to adult care. Common reasons patients transitioned to an adult clinician included feeling too old for their pediatric doctor, following a pediatric provider suggestion, and going to college. Less than half of those respondents received an adult provider recommendation from their pediatric clinician and <15% reported having a transition preparation visit or receiving any type of written transition materials [389]. Although the investigators believe that transition guidelines are important to follow and may bridge the gap between pediatric and adult care, they did not find a significant difference in HbA1c between those patients who felt the most prepared for their transition versus those that did not feel prepared [389].

Caring for T1D is a lifelong commitment that can be both challenging and fear-inducing in patients. In addition to the insulin pump and improved monitoring devices, other novel interventions for furthering the improvement of care are currently being developed, and the use of mobile applications will most likely be a primary focus particularly in children and adolescents. Having teens learn to monitor themselves via a mobile app or other means would potentially smooth the process from pediatric care to adult care during their emerging adult years. Already knowing how to monitor their disease on their own, while with oversight by parents, would be an important first step in gaining independence. The guidelines and recommendations for providers regarding the transition of their patients to adult care should be heavily considered and implemented. A hefty problem, however, is the lack of existing clinical trials determining which methods of transition assistance are best and which are worth funding and implementing in the clinical care setting. Future research should be dedicated to addressing

these shortcomings in the literature, as well as to developing improved techniques for caring for T1D both on the patient's behalf and the provider's.

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